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TOXICOLOGICAL REVIEW

OF

BERYLLIUM AND COMPOUNDS

(CAS No.7440-41-7)

**In Support of Summary Information on the
Integrated Risk Information System (IRIS)**

April 1998

U.S. Environmental Protection Agency
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FOREWORD

The purpose of this Toxicological Review is to provide scientific support and rationale for the hazard identification and dose-response information in IRIS pertaining to chronic exposure to beryllium. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of beryllium and compounds.

In Section 6, EPA has characterized its overall confidence in the quantitative and qualitative aspects of hazard and dose-response (U.S. EPA, 1995a). Matters considered in this characterization include knowledge gaps, uncertainties, quality of data, and scientific controversies. This characterization is presented in an effort to make apparent the limitations of the assessment and to aid and guide the risk assessor in the ensuing steps of the risk assessment process.

For other general information about this review or other questions relating to IRIS, the reader is referred to EPA's Risk Information Hotline at 202-566-1676.

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This document and summary information on IRIS have received peer review both by EPA scientists and by independent scientists external to EPA. Subsequent to external review and incorporation of comments, this assessment has undergone an Agencywide review process whereby the IRIS Program Manager has achieved a consensus approval among the Office of Research and Development; Office of Air and Radiation; Office of Prevention, Pesticides, and Toxic Substances; Office of Solid Waste and Emergency Response; Office of Water; Office of Policy, Planning, and Evaluation; and the Regional Offices.

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Summaries of the external peer reviewers' comments and the disposition of their recommendations are in Appendix B.

1. INTRODUCTION

This document presents the derivation of the noncancer dose-response assessments for oral exposure (the oral reference dose or RfD) and for inhalation exposure (the inhalation reference concentration or RfC), as well as the cancer hazard and dose-response assessments.

The RfD and RfC are meant to provide information on long-term toxic effects other than carcinogenicity. The reference dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as some carcinogenic responses. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The inhalation reference concentration (RfC) is analogous to the oral RfD. The inhalation RfC considers toxic effects for the respiratory system (portal-of-entry) and effects peripheral to the respiratory system (extrarespiratory or systemic effects). It is generally expressed in units of mg/m³.

The carcinogenicity assessment is meant to provide information on three aspects of the carcinogenic risk assessment for the agent in question: the EPA characterization, and quantitative estimates of risk from oral exposure and from inhalation exposure. The characterization reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which any carcinogenic effects may be expressed. Quantitative risk estimates are presented in three ways. The *slope factor* is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg-day. The *unit risk* is the quantitative estimate in terms of either risk per µg/L drinking water or risk per µg/m³ air breathed. The third form is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000.

Development of these hazard identification and dose-response assessments for beryllium has followed the general guidelines for risk assessments as set forth by the National Research Council (1983). Other EPA guidelines that were used in the development of this assessment include the following: the Risk Assessment Guidelines (U.S. EPA, 1987a), the Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996a), Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991a), (proposed) Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity (U.S. EPA, 1994a), (proposed) Guidelines for Neurotoxicity Risk Assessment (U.S. EPA, 1995a), Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (U.S. EPA, 1994b), Recommendations from and Documentation of Biological Values for Use in Risk Assessment (U.S. EPA, 1988), the Use of the Benchmark Dose Approach in Health Risk Assessment (U.S. EPA, 1995b), and Guidance of Risk Classification (U.S. EPA, 1995c).

Literature search strategy employed for this compound was based on the CASRN and at least one common name. As a minimum, the following databases were searched: RTECS, HSDB, TSCATS, CCRIS, GENETOX, EMIC, EMICBACK, ETICBACK, TOXLINE, CANCERLINE, MEDLINE, and MEDLINE backfiles. Any pertinent scientific information

submitted by the public to the IRIS Submission Desk was also considered in the development of this document.

2. CHEMICAL AND PHYSICAL INFORMATION RELEVANT TO ASSESSMENTS

The element beryllium (Be) was discovered in 1798 by the French chemist Vauquelin, who prepared the hydroxide of beryllium. The metallic element was first isolated independently in 1828 by Wohler and Bussy, and the latter named the new element glucinium (Gl) because of the sweet taste of its salts (Bussy, 1828). Today, this name is still used in the French chemical literature. In 1957, Wohler's name "beryllium" was officially recognized by IUPAC (Ballance et al., 1978).

The Chemical Abstracts Service (CAS) names, registry numbers, and respective atomic or molecular formulas for pure beryllium or beryllium compounds are listed along with some alloys of beryllium (IARC, 1980):

| | | |
|--|------------|---|
| Beryllium | 7440-41-7 | Be |
| Acetic acid, beryllium salt | 543-81-7 | Be (C ₂ H ₃ O ₂) ₂ |
| Hexakis[acetato-0:0]-oxotetraberyllium | 19049-40-2 | Be ₄ O(C ₂ H ₃ O ₂) ₆ |
| Bis[carbonato-(2-)]dihydroxytriberyllium | 66104-24-3 | (BeCO ₃) ₂ .Be(OH) ₂ |
| Beryllium chloride | 7787-47-5 | BeCl ₂ |
| Beryllium fluoride | 7787-49-7 | BeF ₂ |
| Beryllium hydroxide | 13327-32-7 | Be(OH) ₂ |
| Beryllium oxide | 1304-56-9 | BeO |
| Phosphoric acid, beryllium salt (1:1) | 13598-15-7 | BeHPO ₄ |
| Phenakite | 13598-00-0 | Be ₂ SiO ₄ |
| Sulfuric acid, beryllium salt (1:1) | 13510-49-1 | BeSO ₄ |
| Silicic acid, beryllium zinc salt | 39413-47-3 | ND |
| Bertrandite | 12161-82-9 | 4BeO.2SiO ₂ .H ₂ O |
| Beryl | 1302-52-9 | 3BeO.Al ₂ O ₃ .6SiO ₂ |
| Aluminum alloy, Al, Be | 12770-50-2 | ND |
| Copper alloy, Cu, Be | 11133-98-5 | ND |
| Nickel alloy, Ni, Be | 37227-61-5 | ND |

ND = Exact composition unknown or undetermined.

Elemental beryllium has many unique physical properties. It is the lightest of all solid and chemically stable substances, with an unusually high melting point of 1,278°C, low density, and very high specific heat, heat of fusion, sound conductance, and strength-to-weight ratio. Beryllium is lighter than aluminum but is more than 40% more rigid than steel.

The chemical properties of beryllium differ considerably from those of the other alkaline earth metals. It has a number of chemical properties similar to aluminum even though the two elements have different oxidation states (Be^{+2} , Al^{+3}) based on their different positions in the periodic table; namely, Groups IIA and IIIA for beryllium and aluminum, respectively. The ionic radius of beryllium is only 0.31 angstroms, with a large ionic charge-to-radius ratio of 6.45. Because of this, the most stable beryllium compounds are formed with smaller anions such as fluoride and oxide (Krejci and Scheel, 1966). This high charge-to-radius ratio of bivalent beryllium also accounts for the amphoteric nature (like aluminum, beryllium behaves as an acid in presence of a base and vice versa) of the ion (Basolo, 1956; Cartledge, 1928) and the strong tendency of beryllium compounds to hydrolyze. The degree of hydrolysis is dependent on the nature of the salt [i.e., $\text{BeF}_2 \sim 1\%$; $\text{BeCl}_2 \sim 4.6\%$] (Drury et al., 1978). In addition to forming various types of ionic bonds, beryllium has a strong tendency for covalent bond formation. For example, it can form organometallics such as $(\text{CH}_3)_2\text{Be}$.

Most metallic salts formed from hydrochloric, hydrofluoric, and nitric acids are very soluble in water; beryllium is no exception. However, anhydrous beryllium sulfate, beryllium hydroxide, beryllium oxide, and beryllium carbonate are for the most part relatively insoluble in water. In hot water, however, anhydrous beryllium sulfate is converted to the tetrahydrate, with a solubility of 425 g/L (Table 1). Aqueous solutions of beryllium salts are acidic as a result of the formation of $\text{Be}(\text{OH}_2)_4^{+2}$, the tetrahydrate. Because of its amphoteric character, beryllium is capable of forming positive ions in dilute acids at a $\text{pH} < 5$ and negative ions called beryllates [$(\text{BeO}_2)^-$] above pH of 8, with insoluble hydroxides and complexes forming between pH 5 and 8 (Drury et al., 1978). Salts of strong bases and weak acids (e.g., beryllium acetate) are capable of hydrolyzing and reacting with water to form insoluble hydroxides. Beryllium is likely to occur in natural waters only in trace quantities ($< 1 \mu\text{g/L}$), since beryllium compounds are relatively insoluble at the pH of natural waters (Hem, 1970). Such is shown in Figure 1, which demonstrates the degradation, fate, and transport of beryllium compounds in any neutral environment. In neutral environments the oxides, sulfates, hydroxides and nitrates, and beryllium oxy organic compounds are shown as forming insoluble beryllium compounds and remain in the particulate, rather than the dissolved, species. The fluorides of beryllium are soluble and will remain in the dissolved state (Dairy et al., 1996). Detectable concentrations of beryllium are found in acidified waters. In view of the increased acidification of some natural waters, there is potential for an increased solubility of beryllium salts.

The use of beryllium in alloys is based on a combination of outstanding properties that are conferred on other metals: low density combined with strength, high melting point, resistance to oxidation, and a high modulus of elasticity. These alloys are suitable as lightweight materials that must withstand high acceleration or centrifugal forces. However, beryllium-rich alloys have not played a significant role because of the brittle nature imparted by beryllium to other metals and the low solubility of most elements in solid beryllium. The only alloy with a high beryllium content is lock-alloy, containing 62% beryllium and 38% aluminum.

Table 1. Physical and chemical properties of beryllium compounds

| | Beryllium oxide | Beryllium sulfate | Beryllium hydroxide | Beryllium carbonate | Beryllium fluoride | Beryllium chloride | Beryllium nitrate |
|------------------------|-----------------|---|---------------------|--|--------------------|--------------------|--|
| Molecular formula | BeO | BeSO ₄ | Be(OH) ₂ | BeCO ₃ + Be(OH) ₂ | BeF ₂ | BeCl ₂ | Be(NO ₃) ₂ •3H ₂ O |
| Molecular weight | 25.01 | 105.07 | 43.03 | 112.05 | 47.01 | 79.93 | 187.07 |
| CAS registry number | 1304-56-9 | 13510-49-1 | 13327-32-7 | 13106-47-3 | 7787-49-7 | 7787-47-5 | 13597-99-4 |
| Specific gravity (20°) | 3.01 | 2.44 | 1.92 | NR | 1.986 (25°) | 1.899 (25°) | 1.557 |
| Boiling point, °C | 3,900 | NR | NR | NR | NR | 482.3 | 142 |
| Melting point, °C | 2,530±30 | Decomposes 550-600 | NR | NR | 555 | 399.2 | 60 |
| Vapor pressure, mm Hg | NR | NR | NR | NR | NR | 1,291°C | NR |
| Water solubility, mg/L | 0.2, 30°C | Insoluble in cold water; converted to tetrahydrate in hot water | Slightly soluble | Insoluble in cold water; decomposes in hot water | Extremely soluble | Very soluble | Very soluble |

Sources: U.S. EPA, 1991b.

NR = Not reported.

| | |
|--|--|
| <p>Ammonium Tetrafluoroberyllate (Ammonium Beryllium Fluoride) $(\text{NH}_4)_2\text{BeF}_4 \rightarrow 2[\text{NH}_4]^+_{\text{aq}} + [\text{BeF}_4]^{2-}_{\text{aq}}$ Excess H_2O pH 7</p> | <p><i>Remains soluble in a neutral environment</i></p> |
| <p>Beryllium Oxide $\text{BeO} + \text{H}_2\text{O} \rightarrow \text{Be}(\text{OH})_2$ Excess H_2O pH 7</p> | <p><i>Forms insoluble beryllium hydroxide in a neutral environment</i></p> |
| <p>Beryllium Hydroxide $\text{Be}(\text{OH})_2 \rightarrow \text{No Reaction}$ Excess H_2O pH 7</p> | <p><i>Beryllium hydroxide is insoluble in a neutral environment</i></p> |
| <p>Beryllium Fluoride $\text{BeF}_2 + 2\text{H}_2\text{O} \rightarrow [\text{BeF}_2(\text{H}_2\text{O})_2]_{\text{aq}}$ and other complexes Excess H_2O pH 7</p> | <p><i>Remains soluble in a neutral environment</i></p> |
| <p>Beryllium Nitrate Trihydrate $\text{Be}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O} + 2\text{MOH} \xrightarrow{\text{Excess H}_2\text{O}} \text{Be}(\text{OH})_2 + 2[\text{M}]^+_{\text{aq}} + 2[\text{NO}_3]^-_{\text{aq}} + 3\text{H}_2\text{O}$ Base Excess H_2O Beryllium Hydroxide Nitrate Salt in Solution pH 7</p> | <p><i>Forms insoluble beryllium hydroxide in a neutral environment</i></p> |
| <p>Beryllium Sulfate Tetrahydrate $\text{BeSO}_4 \cdot 4\text{H}_2\text{O} + 2\text{MOH}^* \xrightarrow{\text{Excess H}_2\text{O}} \text{Be}(\text{OH})_2 + 2[\text{M}]^+_{\text{aq}} + [\text{SO}_4]^{2-}_{\text{aq}} + 4\text{H}_2\text{O}$ Base Excess H_2O Beryllium Hydroxide Sulfate Salt in Solution pH 7</p> <p>*M signifies a cation such as sodium, potassium, calcium, etc.</p> | <p><i>Forms insoluble beryllium hydroxide in a neutral environment</i></p> |
| <p>Beryllium Oxalate Trihydrate $\text{BeC}_2\text{O}_4 \cdot 3\text{H}_2\text{O} + 2\text{MOH} \xrightarrow{\text{Excess H}_2\text{O}} \text{Be}(\text{OH})_2 + 2[\text{M}]^+_{\text{aq}} + [\text{C}_2\text{O}_4]^{2-}_{\text{aq}} + 3\text{H}_2\text{O}$ Base Excess H_2O Beryllium Hydroxide Oxalate Salt in Solution pH 7</p> | <p><i>Forms insoluble beryllium hydroxide in a neutral environment</i></p> |
| <p>Beryllium Basic Acetate* $\text{Be}_4\text{O}(\text{C}_2\text{H}_3\text{O}_2)_6 + 6\text{MOH} + \text{H}_2\text{O} \xrightarrow{\text{Excess H}_2\text{O}} 4\text{Be}(\text{OH})_2 + 6[\text{M}]^+_{\text{aq}} + 6[\text{C}_2\text{H}_3\text{O}_2]^-_{\text{aq}}$ Base Excess H_2O Beryllium Hydroxide Acetate Salt in Solution pH 7</p> <p>*Beryllium basic acetate is not a true basic salt; it is a covalent compound.</p> | <p><i>Forms insoluble beryllium hydroxide in a neutral environment</i></p> |

By R. Hertz Ph.D.-M. Emily Ph.D.-W.M. Dairy - Brush Wellman 1996

Figure 1. Precipitation of beryllium compounds in a neutral (pH 6.5-9.5) environment.

3. TOXICOKINETICS RELEVANT TO ASSESSMENTS

3.1. ABSORPTION

Although inhalation is the primary route of uptake of occupationally exposed persons, no human data are available on the deposition or absorption of inhaled beryllium. With respect to deposition and clearance, particles of beryllium, like other inhaled particles, are governed by important factors such as dose, size, and solubility. Particles formed from volatile emissions as a result of high temperature by either nucleation (where gas molecules come together) or condensation (where gas molecules condense onto an existing particle) tend to be fine, much smaller in size than those produced by mechanical processes in which small but more coarse particles are produced from larger ones. In its *Air Quality Criteria for Particulate Matter* document, EPA (1996b) defines air particles according to a bimodal distribution as fine ($< 1 \mu\text{m}$ aerodynamic equivalent diameter [d_{ae}]) and coarse ($> 2.5 \mu\text{m}$ d_{ae}). Studies concerned with measurement of particulate matter often report such results as PM_{10} , referring to samplers that collect increasing fractions as the particle diameter decreases below $10 \mu\text{m}$ MMAD (d_{ae}). For dosimetric purposes in the respiratory tract, 50% of particles of this d_{ae} will penetrate beyond the larynx.

Beryllium particles produced from anthropogenic processes (more than 99% of beryllium emitted into the atmosphere is the result of oil or coal combustion for electric power generation) are generally emitted as the oxide; namely, BeO (U.S. EPA, 1987b). The inhalation toxicity of insoluble beryllium oxide depends to a great extent on its physical and chemical properties, which can be altered considerably depending on production conditions. It is well known that the toxicity of beryllium oxide is dependent on the particle size, with smaller particles ($< 10 \mu\text{m}$, d_{ae}) able to penetrate beyond the larynx. However, most inhalation studies and occupational exposures involve quite small ($< 1\text{-}2 \mu\text{m}$) BeO particles that would penetrate deeply into the lungs. In inhalation studies with beryllium ores, particle sizes are generally much larger, with deposition occurring in several areas throughout the respiratory tract for particles $< 10 \mu\text{m}$ (d_{ae}). Toxicologically relevant exposure to beryllium appears to be almost exclusively confined to the occupational settings today; however, it should be noted that the similar prevalence of chronic beryllium disease (CBD) in the community compared to workers exposed to much higher levels ($100\text{-}1,000 \mu\text{g}/\text{m}^3$) was attributed to the smaller particle size of beryllium emitted to the outside air compared to beryllium particles inside the plant (Eisenbud et al., 1949; Eisenbud and Lisson, 1983). The temperature at which beryllium oxide is calcined influences its particle size (surface area), solubility, and ultimately its toxicity. Beryllium oxide calcinated at 500°C produces a more toxic oxide than at $1,000^\circ\text{C}$, which has been attributed to its greater specific surface area compared to the material calcined at $1,000^\circ\text{C}$ (Finch et al., 1988; Haley et al., 1989).

Occupational studies also show compound-specific differences in beryllium toxicity, but are less clear about whether beryllium metal or beryllium oxide is more toxic, probably because of variability in particle size or solubility differences. Eisenbud and Lisson (1983) found a higher prevalence of CBD in people who worked with beryllium metal than in those who worked with beryllium oxide, and Sterner and Eisenbud (1951) found a much higher prevalence of CBD in people who worked with beryllium oxide than in those who worked with other beryllium compounds. By contrast, Cullen et al. (1987) found a greater frequency of CBD in workers presumably exposed to beryllium oxide fumes compared to the beryllium metal, but the small

particle size of the fume compared to the beryllium metal dust may have contributed to the higher toxicity in this study.

Natural and anthropogenic emissions of beryllium to the atmosphere are depicted in Table 2 (U.S. EPA, 1987b). Atmospheric beryllium oxide returns to earth through wet and dry deposition. Beryllium, once deposited on land as the oxide, remains bound to the soil within the environmental pH range of 4-8 and does not dissolve in water, thus preventing release to ground water. In addition, beryllium is believed not to biomagnify to any extent within food chains. Beryllium generally enters the water as beryllium oxide and slowly hydrolyzes to beryllium hydroxide [$\text{Be}(\text{OH})_2$], which is insoluble in water. BeO and $\text{Be}(\text{OH})_2$ are almost impervious to attack from dilute acids and alkalis. However, such particles are solubilized by a fluoride source or sources of extremely strong acids ($\text{pH} < 0$) and strong bases ($\text{pH} > 14$). Such solubility in strong acids and bases once again demonstrates the amphoteric nature of this metal as the hydroxide. The estimated average concentration of beryllium in any fresh surface water is 1 $\mu\text{g/L}$ or 1 ppb.

3.1.1. Respiratory Absorption

There are no human data on the deposition and absorption of inhaled beryllium. In animals, beryllium deposited in the lung is cleared slowly, with clearance half-times of days to years, depending on the beryllium compound and, in the case of processed beryllium oxides, on the processing temperature. Initial clearance from the lung, which includes uptake, is typically biphasic, and occurs rapidly via the mucociliary escalator, followed by slower clearance via translocation to the tracheobronchial lymph nodes, alveolar macrophage clearance to the tracheal region, and solubilization of beryllium. The initial rapid and slow phase clearance of particles in the tracheobronchial tree leads to half-times of ~1-60 days and 0.6-2.3 years in rats, respectively. Thus, the amount of beryllium in the lung at any time after exposure depends on the amount deposited and the rate of clearance. In human beings, the residence time for beryllium in the lung may be several years, since appreciable amounts of beryllium have been found in the lung many years after exposure was stopped. Lung clearance of beryllium from the alveoli is more rapid in hamsters than in rats and, in both species, is greater in males than females (Sanders et al., 1975). Clearance is also affected by whether a soluble beryllium compound is capable of ionizing in the lung. Non-ionized soluble forms of beryllium, such as citrate, are cleared from the lungs in about 1-4 days; however, the ionized soluble forms precipitate in lung tissue and simulate particulate matter in behavior. Beryllium excretion occurs primarily in the feces, with a larger percentage in the urine at longer postexposure times, as more beryllium is solubilized and systemically distributed.

As discussed in further detail in Section 4.1, the presence of beryllium in the lung is one criterion used to diagnose CBD. In a study of 20 subjects with suspected CBD, the beryllium concentration in lung tissue ranged from 8 to 1,925 $\mu\text{g/g}$, with an average of 282 $\mu\text{g/g}$ dried tissue (Schepers, 1962). Hasan and Kazemi (1974) defined elevated levels of beryllium in the lung as $> 0.02 \mu\text{g/g}$ dry weight of lung. Beryllium lung burden is not predictive of CBD. Stiefel et al. (1980) found that the average beryllium concentration in the blood of 20 people without occupational exposure was 0.9 ng/g.

Table 2. Natural and anthropogenic emissions of beryllium to the atmosphere

| Emission source | Total U.S. production ^a (10 ⁶ tons/year) | Emission factor (g/ton) | Emissions (tons/year) |
|--------------------------|---|----------------------------|--------------------------|
| Natural: | | | |
| Windblown dust | 8.2 | 0.6 | 5.0 |
| Volcanic particles | 0.41 | 0.6 | 0.2 |
| Total | | | 5.2 |
| Anthropogenic: | | | |
| Coal combustion | 640 | 0.28 | 180 |
| Fuel oil | 148 | 0.048 | 7.1 |
| Beryllium ore processing | 0.008 | 37.5 ^b | 0.3 |
| Total | | | 187.4 |

^aUnits of metric tons.

^bThe production of beryllium ore is expressed in equivalent tons of beryl; the emissions factor of 37.5 is hypothetical.

Source: U.S. EPA, 1987b.

Several authors have investigated the pulmonary and whole-body clearance of beryllium compounds following inhalation exposure. The more soluble compounds, such as beryllium sulfate and beryllium oxide calcined (heated as part of its preparation) at 500°C, are cleared more rapidly than less soluble compounds, such as beryllium oxide, calcined at 1,000°C. The influence of calcining temperature of beryllium oxide on the compound's solubility, toxicity, and clearance is discussed in more detail in Section 4.4. In an experiment with beagle dogs exposed for 5-42 min to beryllium oxide calcined at 500 or 1,000°C, Finch et al. (1990) found that pulmonary clearance of both forms from 4 days through 1 year after exposure was described by a single component exponential function. The half-time for pulmonary clearance was 64 days for beryllium oxide calcined at 500°C and 240 days for beryllium oxide calcined at 1,000°C. Whole-body clearance was biphasic for the low-temperature calcined material, with 59% of the initial lung burden cleared with a half-life of 54 days and the half-life for the long-term component being more than 1,000 days. The long-term component was attributed to beryllium that dissolved from particles and bound to extrapulmonary compartments such as the skeleton and liver. Whole-body clearance of beryllium oxide calcined at 1,000°C could be described by a single-component exponential function with a half-life of 310 days. After an interval of 2.5 years, these dogs received a second acute exposure (< 1 h) to beryllium oxide calcined at 500°C, and the whole-

body clearance time was similar to that seen for 500°C BeO in the initial exposure (Haley et al., 1992).

Rhoads and Sanders (1985) observed biphasic lung clearance in rats exposed for 30-180 min to beryllium oxide fired at 1,000°C. The first component accounted for 30% of the initial lung burden and had a half-life of 2.5 days. The second component had a half-life of 833 days. They found that whole-body clearance was uniphasic, with a half-life of 356 days. Sanders et al. (1975) reported an alveolar retention half-life for beryllium oxide of approximately 6 mo in rats and hamsters exposed to beryllium oxide calcined at 1,000°C. Hart et al. (1984) exposed male F344 rats to 447 $\mu\text{g Be/m}^3$ as beryllium oxide heat-treated at 560°C and found rapid clearance of beryllium from the lavageable lung compartment (fluids and free lung cells, half-time < 2 days) but minimal clearance in 21 days from the nonlavageable compartment (lung tissue).

The accumulation of beryllium in the lung was measured in male and female Sprague-Dawley rats exposed to 34.25 $\mu\text{g Be/m}^3$ as beryllium sulfate for 7 h/day, 5 days/week for up to 72 weeks, with three of each sex sacrificed monthly during exposure (Reeves and Vorwald, 1967). The lung burden tended to plateau in both sexes after about 36 weeks. This plateau was attributed to the attainment of an equilibrium between deposition and clearance for this soluble salt. The concentration of beryllium in the tracheobronchial lymph nodes peaked at about 44 weeks, with markedly higher levels in males. This was interpreted as better lymphatic clearance of the lungs in males. Over half of the beryllium in the lungs was still present at 4 weeks after the end of exposure. The study authors suggested that soluble beryllium salts become sequestered in inflammatory scar tissue, or that insoluble precipitates are formed.

Clearance of beryllium chloride, a soluble beryllium salt, is faster than that of the oxide. Hart et al. (1980) exposed guinea pigs for 55 min nose-only to 230 $\mu\text{g Be/m}^3$ as beryllium chloride. Immediately after the end of exposure, 34% of the initial body burden was in the gastrointestinal tract, indicating significant mucociliary clearance during exposure. By 48 h postexposure, 50% of the initial lung burden had been removed by mucociliary clearance or alveolar clearance. However, 34% of the initial body burden was still present at 14 days, primarily in the lungs, indicating that clearance is biphasic. In dogs exposed to 191 $\mu\text{g Be/m}^3$ as beryllium fluoride for 6 h/day, 5 days/week for various exposure durations, the rate of increase of the beryllium level in lungs and pulmonary lymph nodes increased with duration of exposure, suggesting decreased clearance (Stokinger et al., 1953). In the lung, beryllium accumulation was 0.013, 0.089, and 0.062 $\mu\text{g/g lung/day}$ for 47, 87, and 207 days of exposure, respectively. A continuous increase in the rate of beryllium accumulation was observed in the pulmonary lymph nodes.

There is evidence that the initial lung burden does not affect the pulmonary clearance of beryllium but does affect the clearance of other particles. No significant differences in beryllium lung clearance half-times (250-380 days) were noted among male F344/N rats receiving inhalation exposure to beryllium metal aerosol resulting in initial lung burdens of 1.8, 10, or 100 μg (Finch et al., 1994). Exposure was to 4.7-150 mg/m^3 for 14-30 min. (Additional animals received an initial lung burden of 0.32 μg , but clearance could not be calculated for this dose.) However, there was a dose-related decrease in the clearance of a radioactive tracer particle. The reason for a dose-related effect on the tracer particle, but no dose-related effect on clearance of beryllium

itself, is unclear. However, the study authors suggest that the beryllium particles might be sequestered at the sites of inflammation and thus shielded from normal clearance mechanisms. Sanders et al. (1975) found that clearance of a radioactive tracer was decreased by 40% for at least 60 days postexposure in female rats receiving an initial alveolar deposition of 30 μg beryllium as beryllium oxide calcined at 1,000°C (exposure level and duration not reported).

3.1.2. Gastrointestinal Absorption

Gastrointestinal absorption can occur by both the inhalation and oral (diet, drinking) routes of exposure. In the case of inhalation, a portion of the inhaled material is transported to the GI tract by the mucociliary escalator or by the swallowing of the insoluble material deposited in the upper respiratory tract (Kjellstrom and Kennedy, 1984). Unlike inhalation, where a significant part of the inhaled dose is incorporated into the skeleton (ultimate site of beryllium storage, half-life of 450 days), oral administration results in < 1% absorption and storage (as reviewed by U.S. EPA, 1991b). Most of the beryllium taken up by the oral route passes through the gastrointestinal tract unabsorbed and is eliminated in the feces.

3.1.3. Dermal Absorption

Dermal absorption, like oral, contributes only very small amounts to the total body burden of beryllium-exposed persons; however, because of the skin effects elicited by beryllium compounds, this route is of some significance. Since most beryllium salts do not remain soluble at physiological pH, there is no ready systemic diffusion following local skin contact because beryllium is bound by epidermal (alkaline phosphatase and nucleic acids) constituents.

3.2. DISTRIBUTION

Beryllium in animals is cleared from the lung and distributed primarily in the skeleton, with additional deposition in tracheobronchial lymph nodes. After a single 5- to 42-min exposure of beagle dogs to beryllium oxide calcined at 500°C, 14% and 16% of the initial lung burden was found in the skeleton at 64 and 180 days postexposure, respectively (Finch et al., 1990). At 180 days, comparable levels were in the lung and skeleton. The amount of beryllium in the tracheobronchial lymph nodes peaked at 8.8% of the initial lung burden at 64 days postexposure, and the amount of beryllium found in the liver increased with time. By contrast, for the material calcined at 1,000°C, 88%, 1.9%, and 1.5% of the initial lung burden was found in the lungs, tracheobronchial lymph nodes, and skeleton, respectively, at 64 days postexposure. In dogs exposed by inhalation to beryllium fluoride, beryllium sulfate, or beryllium oxide, Stokinger et al. (1953) found beryllium primarily in the lung, pulmonary lymph nodes, skeleton, and liver. The more soluble compounds (the fluoride and sulfate) had a larger percentage of the total body burden in the skeleton and liver, indicating greater systemic distribution. Rats sacrificed 3 weeks after receiving a single intratracheal instillation of radiolabeled beryllium oxide calcined at 1,000°C had beryllium primarily in the lung, with much smaller amounts in the liver, kidney, femur, and heart (Clary et al., 1975). Sanders et al. (1975) found that deposition in

tracheobronchial lymph nodes increased with time after inhalation exposure to beryllium oxide calcined at 1,000°C.

3.3. ELIMINATION AND EXCRETION

Excretion of unabsorbed beryllium is primarily via the fecal route shortly after exposure (inhalation or intratracheal) through mucociliary clearance from the respiratory tract and ingestion of swallowed beryllium (Hart et al., 1980; Finch et al., 1990). Urinary excretion becomes more important at later time points, especially for the more soluble beryllium compounds, as absorbed beryllium is removed from the body. Beryllium oxide calcined at 1,000°C is less soluble, and fecal excretion dominated at all time periods in dogs through 1 year after exposure (Finch et al., 1990). At 32 days after an acute inhalation exposure of beagle dogs, fecal excretion accounted for 59% of total excretion of beryllium oxide calcined at 500°C, and 68% for beryllium oxide calcined at 1,000°C (Finch et al., 1990). By 180 days postexposure, fecal excretion accounted for 47% of total excretion of the low-fired material and 54% of total excretion for the high-fired material. In guinea pigs exposed to 230 µg Be/m³ as beryllium chloride for 55 min, Hart et al. (1980) described a 40% reduction of beryllium body burden within 48 h, primarily by fecal excretion (90%). Rhoads and Sanders (1985) reported that virtually all excreted beryllium was in the feces, following a single inhalation exposure of rats to beryllium oxide calcined at 1,000°C.

Andre et al. (1987) measured excretion of beryllium metal powder and of hot-pressed (at 1,000°C) beryllium metal after intratracheal instillation in *Papio papio* baboons and rats. Urinary excretion showed a clear relationship to the amount of beryllium instilled. Mean daily excretion of beryllium metal was $4.6 \times 10^{-6}\%$ of the administered dose in baboons and $3.1 \times 10^{-6}\%$ in rats. Hot-pressed beryllium was more soluble, with a daily excretion of $13.8 \times 10^{-6}\%$ of the dose in rats.

Urinary excretion of beryllium following occupational exposure correlates qualitatively with the degree of exposure but does not correlate with the severity of CBD (Klemperer et al., 1951). The average daily excretion of beryllium in a group of former beryllium workers ranged from 1.2 to 8.3 µg/L with an average of 4.0 µg/L. Stiefel et al. (1980) reported 2 µg/L beryllium in the urine of smokers who used unfiltered cigarettes; no information was provided on urinary levels in nonsmokers without occupational exposure. The average urinary beryllium level in dental technicians exposed to beryllium was 0.37 µg/L, while the average in the general population in an area with a high density of metallurgical manufacturing industries was 0.24 µg/L (Apostoli et al. 1989).

Soluble beryllium appears to cross the placenta, based on findings in mice injected intravenously with approximately 0.1 mg/kg radiolabeled beryllium chloride (Bencko et al., 1979).

4. HAZARD IDENTIFICATION

4.1. STUDIES IN HUMANS—EPIDEMIOLOGY, CASE REPORTS, AND CLINICAL CONTROLS

There is an extensive database of occupational studies that have examined the basis for two principal health concerns of beryllium compounds: chronic beryllium disease and lung cancer. In 1952, a Beryllium Case Registry (BCR) was established to provide a central source for cases of diagnosed beryllium poisoning (acute berylliosis or chronic beryllium disease). The criteria for entry in the BCR included either documented past exposure to beryllium or the presence of beryllium in lung tissue as well as clinical evidence of beryllium disease.

4.1.1. Chronic Beryllium Disease

Chronic beryllium disease (CBD), formerly known as “berylliosis” or “chronic berylliosis,” is an inflammatory lung disease that results from inhalation exposure to beryllium. It is characterized by the formation of granulomas (pathologic clusters of immune cells) with varying degrees of interstitial fibrosis, and involves a beryllium-specific immune response. A particularly important part of the diagnosis of CBD is to distinguish it from sarcoidosis, a granulomatous lung disease of unknown cause. The beryllium case registry lists the following criteria for diagnosing CBD:

(1) Establishment of significant beryllium exposure based on sound epidemiologic history; (2) Objective evidence of lower respiratory tract disease and clinical course consistent with beryllium disease; (3) Chest X-ray films with radiologic evidence of interstitial fibronodular disease; (4) Evidence of restrictive or obstructive defect with diminished carbon monoxide diffusing capacity (DL_{CO}) by physiologic studies of lung function; (5a) Pathologic changes consistent with beryllium disease on examination of lung tissue; and (5b) Presence of beryllium in lung tissue or thoracic lymph nodes.

Cases were entered into the registry if they met at least three of the criteria (Hasan and Kazemi, 1974).

The criteria for diagnosis of CBD have evolved with time, as more advanced diagnostic technology has become available. These varying definitions of CBD should be considered in comparing results from different studies. More recent criteria have both higher specificity than earlier methods and higher sensitivity, identifying subclinical effects. Recent studies typically use the following criteria: (1) history of beryllium exposure; (2) histopathological evidence of noncaseating granulomas or mononuclear cell infiltrates in the absence of infection; and (3) a positive blood or bronchoalveolar lavage (BAL) lymphocyte transformation test (Newman et al., 1989). The availability of transbronchial lung biopsy facilitates the evaluation of the second criterion, by making histopathological confirmation possible in almost all cases.

A key aspect of the identification of CBD is the demonstration of beryllium sensitization in the beryllium lymphocyte transformation test (BeLT, also known as the LTT, BeLPT) (reviewed by Newman, 1996). In this test, lymphocytes obtained from either BAL fluid or from peripheral blood are cultured in vitro and then exposed to soluble beryllium sulfate to stimulate lymphocyte proliferation. The observation of beryllium-specific proliferation indicates beryllium sensitization. Early versions of the test had high variability, but the use of tritiated thymidine to identify proliferating cells has led to a more reliable test (Mroz et al., 1991; Rossman et al., 1988). In recent years, the peripheral blood test has been found to be as sensitive as the BAL assay, although larger abnormal responses are generally observed in the BAL assay (Kreiss et al., 1993a; Pappas and Newman, 1993). False negative results can occur with the BAL BeLT in cigarette smokers who have marked excess of alveolar macrophages in lavage fluid (Kreiss et al., 1993a). The BeLT has also been used in animal studies to identify those species with a beryllium-specific immune response (see Section 4.4). As described below, the BeLT test can detect beryllium sensitization and has a higher predictive value in CBD screening than clinical exam, spirometry, or chest radiography.

Evaluation of the exposure-response to beryllium has been made more difficult because, as described below, CBD is an immune disease, and only a small percentage of the population appears to be susceptible. Nonetheless, exposure-response relationships are evident. Several studies have observed CBD in people chronically exposed in modern plants, which are generally in compliance with the beryllium permissible exposure limit of $2 \mu\text{g}/\text{m}^3$.

Kreiss et al. (1996) conducted a cross-sectional study of 136/139 of then-current beryllium workers in a plant that made beryllia ceramics from beryllium oxide powder. An additional 15 workers who had been exposed to beryllium at other jobs were excluded from exposure calculations because their earlier exposure was not known. Because the plant opened in 1980, high-quality industrial hygiene measurements were available for almost the entirety of the exposure period. Measurements from 1981 and later were reviewed and included area samples, process breathing-zone samples, and personal lapel samples (the last year only). Quarterly daily-weighted average (DWA) exposures were calculated using a formula based on all of these measurements for each job title. However, general area and breathing zone samples were not recorded for machining processes until the last quarter of 1985, soon after machining production was transferred to that plant, even though a limited amount of machining had been conducted since 1982. Although total beryllium exposure was generally well characterized for most of the affected workers, two of the seven beryllium-sensitized machinists started machining prior to the systematic environmental monitoring. Since exposure levels generally declined with time, exposure estimates for these two subjects may have been underestimated. The median breathing zone measurement of beryllium for machining was $0.6 \mu\text{g}/\text{m}^3$, and $0.3 \mu\text{g}/\text{m}^3$ for other processes. The frequency of excursions to higher exposure levels decreased with time, with the percentage of machining breathing zone measurements above $5 \mu\text{g}/\text{m}^3$ falling from 7.7% during early sampling years to 2.1% during later sampling years.

Beryllium lymphocyte transformation tests were performed by 2 different laboratories on blood samples collected from 136 employees. Positive results from one or both laboratories were confirmed by analyzing a subsequent blood sample. Of 136 tested employees, 5 had consistently abnormal blood BeLT results and were diagnosed with CBD based on observation of granulomas

in lung biopsy samples. An additional two employees had abnormal blood results from one of the two laboratories and had no granulomas in lung biopsy samples. Both employees developed abnormal blood results in other laboratory tests within 2 years. One of these two employees also developed symptoms of CBD. The other employee declined clinical follow-up. An additional case of CBD was found during the study in an employee hired in 1991, who had a nonhealing granulomatous response to a beryllium-contaminated skin wound. This subject had a confirmed abnormal blood test and after several additional months developed lung granulomas. Only one CBD case had an abnormal chest X-ray (defined as small opacity profusion of 1/0 or greater). An additional 11 former employees had CBD, for a total prevalence of 19/709. Beryllium-sensitized cases were similar to nonsensitized ones in terms of age, ethnic background, and smoking status, but did have significantly fewer pack-years of smoking. There was also no significant difference in percent exposed to beryllium dust or mist in an accident or unusual incident, or those in areas with a posted high air count. Of the eight sensitized workers, seven had worked in machining at some point, while one had never worked in a production job. The beryllium sensitization rate was 14.3% among the machinists, compared to 1.2% among all other employees. The individual average beryllium exposures for the six CBD cases and two sensitized cases among current employees ranged from 0.2 to 1.1 $\mu\text{g}/\text{m}^3$, and the cumulative exposure ranged from 92.6 to 1,945 $\mu\text{g}/\text{m}^3$ -days. The median of estimated average beryllium exposure for the sensitized cases was about 0.55 $\mu\text{g}/\text{m}^3$. The sensitized cases without disease did not have lower exposures than the CBD cases. Machinists may have been more susceptible than other groups because of their higher overall exposure, or because the particles produced during machining were primarily respirable in size, while other exposures were to particles larger than the respirable range. Other characteristics of the machining exposure, such as the particle morphology and surface properties or adjuvants in machining fluids, may also have affected sensitization. The study authors noted that median breathing zone levels tended to be lower than the DWAs derived from these levels, because much of the day was typically spent in high-exposure tasks. This study identified a lowest-observed-adverse-effect level (LOAEL) of 0.55 $\mu\text{g}/\text{m}^3$, and a LOAEL Human Equivalent Concentration (LOAEL[HEC]), adjusted for an occupational exposure (5 days/7 days, 10 m^3 per 8-ho workday/20 m^3 per day), of 0.20 $\mu\text{g}/\text{m}^3$.

Cullen et al. (1987) reported five likely cases of CBD (using the beryllium case registry definition of CBD) in workers who were presumably exposed to beryllium oxide fumes at a precious metals refinery for 4-8 years before the development of symptoms. Time-weighted average personal air samples for beryllium ranged from 0.22 to 42.3 $\mu\text{g}/\text{m}^3$ throughout the plant, and 10% of the samples were $> 2.0 \mu\text{g}/\text{m}^3$. However, four of the cases worked predominantly in the furnace area, where beryllium exposure was measured at $0.52 \pm 0.44 \mu\text{g}/\text{m}^3$ (maximum measurement 1.7 $\mu\text{g}/\text{m}^3$). No additional cases were found in the screening of current workers, but a fifth was identified after the screen. This subject worked as a crusher, where exposure was to beryllium metal dust at $2.7 \pm 7.2 \mu\text{g}/\text{m}^3$. The CBD cases had the classic signs of CBD, including hilar adenopathy visible radiologically, noncaseating granuloma and pulmonary fibrosis in biopsy samples, and decreased DL_{CO} . Symptoms progressed even after the removal from exposure. Beryllium sensitization was shown in vitro with BAL lymphocytes. Three of the cases were considered to have CBD, while diagnosis of two (both in the furnace area) was complicated by confounding factors. One had a history of hilar enlargement and the other had schistosomiasis and no BAL stimulation data. The study authors also analyzed beryllium exposure levels by job classification and screened 45 of 70 current workers for CBD using interviews and analysis of

spirometry data and chest radiographs from routine testing. No in vitro screening for beryllium sensitization was conducted on the general worker population. Noting that the prevalence of CBD was highest at a task with a lower exposure levels, the study authors suggested that the beryllium oxide fumes to which workers were exposed in the furnace area were more toxic than the beryllium metal dust to which workers were exposed at other tasks. The study authors considered alternative explanations for the development of disease following low-level exposure to be unlikely. Although sampling efficiency was less than 100% for particles < 0.8 microns, these small particles were not considered to contribute significantly to the overall mass. However, such small particles may be even more toxic because of their large surface area per unit mass. There was concomitant exposure to arsenic at $0.82 \pm 0.26 \mu\text{g}/\text{m}^3$, cadmium at $38.9 \pm 27.2 \mu\text{g}/\text{m}^3$, lead at $20.3 \pm 15.2 \mu\text{g}/\text{m}^3$, and nickel at $91.9 \pm 67.6 \mu\text{g}/\text{m}^3$, but these levels were all within acceptable exposure limits. Although the study authors note that there have been no significant changes in work practices during the past 20 years, it is possible that the small number of retrospective air samples collected in a 2-week period may not accurately reflect past and present exposure conditions. The LOAEL in this study was $0.52 \mu\text{g}/\text{m}^3$, with a LOAEL (HEC) after adjusting for occupational exposure of $0.19 \mu\text{g}/\text{m}^3$.

Stange et al. (1996) assessed beryllium sensitization and CBD in 1,885 current employees and 2,512 former employees at the Rocky Flats Environmental Technology site. Beryllium concentrations in the main beryllium production building were measured from 1970 to 1988 using fixed airhead samplers and from 1984 to 1987 using personal air monitoring devices. The mean beryllium concentrations from fixed airhead samplers and personal monitoring devices were $0.16 \mu\text{g}/\text{m}^3$ (95% confidence interval of $0.10\text{-}0.22 \mu\text{g}/\text{m}^3$) and $1.04 \mu\text{g}/\text{m}^3$ (95% confidence interval of $0.79\text{-}1.29 \mu\text{g}/\text{m}^3$), respectively. Beryllium sensitization (positive blood BeLT results from 2 different laboratories or positive results in two consecutive blood BeLTs) was diagnosed in 22 current employees (1.2%) and 47 former employees (1.9%). CBD was diagnosed in 6 (0.3%) and 22 (0.9%) current and former employees, respectively. The combined incidence of CBD and beryllium sensitization was 1.49% and 2.75% among the current and former employees (2.21% for both groups combined). Current and former employees with negative BeLT results or unconfirmed positive results were retested 3 years later, along with employees not participating in the previous screening and employees with abnormal X-rays; employees with no definitive diagnosis of CBD were offered a BeLT and chest X-ray 1 year after the initial screening. The 3- and 1-year retesting resulted in a beryllium sensitization and CBD incidence of 9/518 (1.7%) and 1/518 (0.2%), respectively. The total incidence of beryllium sensitization and CBD among the current and former employees (includes cases from initial and follow-up screenings) was 107/4,397 (2.43%). A total of 29 cases of CBD were diagnosed among the current and former employees at the Rocky Flats site: 17 cases had evidence of granulomas on biopsy, 7 had no evidence of granulomas, and biopsies were not performed for 5 cases. Thus, this study identified a LOAEL of $1.04 \mu\text{g}/\text{m}^3$ for beryllium sensitization and CBD; the LOAEL(HEC) after adjusting for occupational exposure is $0.37 \mu\text{g}/\text{m}^3$.

Cotes et al. (1983) evaluated beryllium exposure and its effects in 130 of the 146 men who had worked at a beryllium manufacturing plant for at least 6 mo. Exposure was measured as area samples, and the geometric mean concentration for each sample site and year was estimated by eye after plotting the data on logarithmic graph paper. Mean exposure for different job processes was $0.029\text{-}0.72 \mu\text{g Be}/\text{m}^3$ as beryllium oxide in 1952, and $0.022\text{-}0.21 \mu\text{g Be}/\text{m}^3$ in 1960. Four

definite clinical cases of CBD, one highly probable case of CBD, and two cases of radiographic abnormality were identified. The definition of CBD was not reported, but two of the definite cases were described as having typical radiographic and lung function changes but no overt clinical symptoms. Two other cases of "subacute" beryllium disease were identified in follow-up studies, one of whom developed CBD after a beryllium patch test. The probable cases had small radiographic opacities with no other explanation, and one had a somewhat reduced DL_{CO} . The two definite cases identified in the main study worked entirely in the slip-casting bay, where the geometric mean beryllium concentration was $0.036 \mu\text{g}/\text{m}^3$ in 1952 and $0.18 \mu\text{g}/\text{m}^3$ in 1960. Their exposure duration was about 6 years. The overall average exposure levels were not reported. However, based on the reported months of exposure and cumulative exposure level, the average exposure can be estimated as $0.1 \mu\text{g}/\text{m}^3$ for the two definite cases and 0.05 - $0.16 \mu\text{g}/\text{m}^3$ for the cases of radiographic changes only. There was no evidence of an association between CBD and brief high exposures. Seventeen men at the plant recalled brief periods of high exposure and two developed acute beryllium disease, but none of these men developed CBD. This study is limited by the poor description of the definition used for CBD, but it identifies a LOAEL of $0.1 \mu\text{g}/\text{m}^3$, corresponding to a LOAEL(HEC) of $0.036 \mu\text{g}/\text{m}^3$.

Few data are available on the particle characteristics of beryllium under occupational exposure conditions. However, Hoover et al. (1990) found that 5.7% of the particles released during sawing of beryllium metal had aerodynamic diameters smaller than $25 \mu\text{m}$ but larger than $5 \mu\text{m}$, and 0.3% were smaller than $5 \mu\text{m}$. For milling of beryllium metal, 12% to 28% of the particles had aerodynamic diameters between 5 and $25 \mu\text{m}$, and 4% to 9% were smaller than $5 \mu\text{m}$, depending on the milling depth. More than 99% of the particles generated from operations conducted with beryllium alloys were larger than $25 \mu\text{m}$.

CBD has been reported in people not occupationally exposed to beryllium, including people living in communities near beryllium plants (Chesner, 1950; Dattoli et al., 1964; Lieben and Metzner, 1959) and in families of beryllium workers who wore contaminated clothing at home. These cases have been markedly reduced by better industrial hygiene, including mandatory work clothes exchange, but nonoccupational CBD has still been reported following low-level episodic exposure of family members (Newman and Kreiss, 1992).

The most complete investigation of community cases of CBD was conducted by Eisenbud et al. (1949), who evaluated exposure related to 11 cases of CBD based on radiographic and pathologic examination. Radiologic screening of 10,000 residents was conducted, with questionable cases undergoing clinical evaluation. CBD was diagnosed based on radiologic and clinical findings and on a consensus of specialists. One case was exposed to beryllium dust on worker clothes and will not be discussed further. Of the other cases, five lived within 0.25 miles of a beryllium production plant, and all lived within 0.75 miles of the plant. A follow-up to this study reported three additional cases at less than 0.75 miles from the plant but no additional cases of CBD at greater than 0.75 miles (Sterner and Eisenbud, 1951). Measurements downwind from the plant found that the beryllium concentration at 0.75 miles was about $0.045 \mu\text{g}/\text{m}^3$, and continuous sampling stations found that the average concentration at about 700 feet from the plant (the furthest distance within the affected area) was $0.05 \mu\text{g}/\text{m}^3$ (range 0 - $0.46 \mu\text{g}/\text{m}^3$). The emitted beryllium was primarily as beryllium oxide, although beryllium fluoride and beryl (beryllium ore) were also present. The study authors also calculated an estimated exposure, based

on emissions levels, stack heights and windspeed data. These estimates were generally in good agreement with the downwind data. Based on these calculations, the authors estimated that the average exposure levels at 0.75 miles from the plant during the period of exposure monitoring were 0.004-0.02 $\mu\text{g}/\text{m}^3$. Averaging this value to 0.01 $\mu\text{g}/\text{m}^3$ and noting that both plant production and emissions were about 10-fold higher in earlier years, the authors estimated that the concentration at 0.75 miles was 0.01-0.1 $\mu\text{g}/\text{m}^3$. However, the only population data available are within 0.25 miles of the Lorain plant. Eisenbud and Lisson (1983) were quite certain that a population of approximately 500 people was exposed to levels of 0.1 $\mu\text{g}/\text{m}^3$. Beyond 0.25 miles, estimates of exposure are very uncertain. The similar prevalence of CBD in the community compared to workers exposed to much higher levels (up to 100 $\mu\text{g}/\text{m}^3$) was attributed to the smaller particle size of beryllium emitted to the outside air compared to beryllium particles inside the plant (as discussed in Eisenbud and Lisson, 1983). Thus, this study establishes a NOAEL(HEC) of 0.01-0.1 $\mu\text{g}/\text{m}^3$ for the development of CBD in a population exposed to beryllium in ambient air.

The development of fiber-optic bronchoscopy and transbronchial biopsy methods has allowed the identification of subclinical cases of CBD. Newman et al. (1989) evaluated respiratory symptoms and physical examination results in 12 cases of newly identified CBD based on the following: (1) a history of beryllium exposure; (2) histopathological evidence of noncaseating granulomas or mononuclear cell infiltrates; and (3) a positive blood or BAL BeLT. Eight of the cases were exposed to beryllium oxide dust or beryllium fumes (exposure duration of 1-25 years). The other four were exposed primarily to beryllium oxide dust (exposure duration of 0.1-5 years, none with current exposure). Only five sought medical attention for respiratory symptoms and none had systemic symptoms associated with CBD, although at least one had mild respiratory symptoms that were observed in a detailed physical examination. Five of the subjects also had no increase over normal in interstitial markings on chest radiography. Lung volumes and flow rates were abnormal in only 4/12 cases, and oxygen exchange during exercise was abnormal in only 3/9. Based on these findings, the authors suggested that CBD be classified into the following stages: (1) sensitization; (2) subclinical beryllium disease (sensitized subjects with histopathological evidence, but no clinical signs); and (3) beryllium lung disease (same as [2], but with respiratory symptoms, changes on chest radiographs, or altered pulmonary physiology).

Varying, and generally low, prevalences of CBD have been observed in occupationally exposed populations, even when exposure was as high as 100 $\mu\text{g}/\text{m}^3$ (Sterner and Eisenbud, 1951). However, the BeLT has allowed the identification of an exposure-response relationship for beryllium sensitization. Kreiss et al. (1993a) used the BeLT test to evaluate a stratified random sample of nuclear weapons workers ($n = 895$), but the author did not report exposure levels. Subjects with beryllium sensitization underwent further clinical testing, including a lung biopsy and a BAL BeLT test. Of 18 sensitized subjects, 12 had CBD and 3 others developed CBD within 2 years. The sensitization rate correlated with participant-reported exposure level and ranged from 1.5% in the no-exposure group (some of whom had suspected exposures) to 3.4% in the consistent exposure group; machinists (a job title with consistent exposure) had an even higher sensitization rate (4.7%). Longer term longitudinal studies are necessary to determine whether all sensitized subjects eventually develop CBD. The beryllium-sensitized machinists had a longer time since first exposure than the nonsensitized machinists, suggesting that earlier exposures were higher or that the latency period was not sufficient for all cases of

sensitization to have developed in the latter group. Beryllium sensitization, and then CBD, was also detected in a secretary, indicating that a transient, possibly high exposure to beryllium can cause sensitization. Beryllium sensitization was observed to progress to CBD even in the absence of continued exposure, suggesting that abnormal BeLT test findings are predictive of future development of CBD.

Kreiss et al. (1989) used the peripheral blood BeLT to screen an occupationally exposed population for CBD and found that 6/51 (11.8%) of the currently exposed workers were sensitized. One of the sensitized workers had an equivocal BeLT result and did not have CBD, based on the lack of granulomas on transbronchial lung biopsy. Historically, exposure at this plant was to beryllium oxide dust and fumes, but exposure at the time of the study was only to beryllium oxide dust. In a screen of 505 workers at a plant that had manufactured ceramics from beryllium oxide (beryllia) from 1958 through 1975, the prevalence of CBD among various exposed subgroups ranged from 2.9% to 15.8% (Kreiss et al., 1993b). Two cases of CBD that were identified on the basis of chest radiographs had normal or inconsistently abnormal blood BeLT results. No sensitized cases who had not yet developed CBD were identified, perhaps because of the long period since first exposure (23.7 years on average). The latency for CBD ranges from a few months to more than 20 years (Kreiss et al., 1993a). There is at present no clear relationship between exposure duration and the development of the disease. Cases have developed following exposures as short as a few months (Kreiss et al., 1996). Studies suggest that early stages of CBD can be reversed (Rom et al., 1983; Sprince et al., 1978), although these studies are weakened by methodological limitations, as described in the following paragraphs.

Although subjects identified based on BeLT test results may not have overt symptoms of CBD, many do exhibit functional impairment. Pappas and Newman (1993) measured spirometry, lung volumes, arterial blood gases, carbon monoxide diffusing capacity (DL_{CO}), and exercise physiology in a group of 21 workers identified using the blood BeLT ("surveillance-identified") and 15 workers identified based on symptoms or radiographic abnormalities ("clinically identified"). Exercise physiology was the most sensitive test, with 52% of the surveillance-identified subjects exhibiting abnormal pulmonary physiology at maximum exercise; 93% of the clinically identified subjects showed similar abnormalities. Present and former smokers were included in the groups. DL_{CO} was a less sensitive measure. The study authors noted that most of the subjects exhibited a rise in the ratio of dead space to tidal volume (V_D/V_T), even though most subjects had a normal recruitment of V_T . They suggested that this indicates that a pulmonary vascular abnormality occurs early in CBD. As support, they noted that granulomas and fibrosis developing early in the course of the disease are often located in the interstitium in a perivascular distribution.

The clinical severity of CBD, measured by pulmonary function, exercise physiology, and degree of radiographic abnormalities, is reflected by the stimulation index in the BAL BeLT, the BAL white cell count, and the BAL differential cell count (Newman et al., 1994a). Interestingly, the blood BeLT results did not correlate with severity of CBD. Eight subjects without CBD were beryllium-sensitized, as demonstrated by abnormal results in the blood test but normal BAL BeLT results and no evidence of granulomas. These results are consistent with other data (Kreiss et al., 1993a) showing that sensitization precedes inflammatory infiltration of the lung.

A number of studies have characterized the signs and symptoms of CBD. Initial symptoms of early cases of CBD typically include dyspnea, cough, fatigue, weight loss, and chest pain (Aronchik, 1992; Hasan and Kazemi, 1974; Kriebel et al., 1988a; Meyer, 1994; Sterner and Eisenbud, 1951; Williams, 1993). Other symptoms included bibasilar crackles, clubbing of the fingers and skin lesions, heart failure, and an enlarged liver or spleen. Prominent diagnostic findings are diminished vital capacity, diffuse infiltrates, and hilar adenopathy visible radiographically. Fibrosis occurs at late stages in the disease. Granulomatous inflammation has also been reported in extrapulmonary sites, such as extrapulmonary lymph nodes, skin, liver, spleen, kidney, bone, myocardium, central nervous system, and skeletal muscle. As noted above, clinical, radiographic, and traditional spirometric signs of CBD are less sensitive than histologic findings and immunologic screens using the BeLT. Computed tomography (CT) can identify some CBD cases missed by chest radiography, but even CT missed 25% of histologically confirmed cases (Newman et al., 1994b).

Kanarek et al. (1973) measured 1971 beryllium exposure levels and respiratory effects in 214 of 245 full-time workers who were employed for 1 to 14 years at a beryllium extraction and processing plant. Because most operations occurred only during a small fraction of the day, the study authors considered peak air concentrations more important than TWAs, and reported only the former value. Measured beryllium concentrations ranged from 0.31 to 1,310 $\mu\text{g}/\text{m}^3$, with the lower levels corresponding to times that the operations were not occurring. For some processes, the lower range was as high as 7 $\mu\text{g}/\text{m}^3$. They identified 31 workers with radiographic findings consistent with interstitial disease, 20 workers with significant hypoxemia (decreased arterial oxygen tension, Pa_{O_2}), and 11 workers with both symptoms. Two cases of CBD were identified, but screening for CBD was incomplete because biopsies were conducted on only these two subjects. A follow-up study was conducted in 1974, after exposure levels had been markedly reduced, with peak beryllium concentrations of 15 $\mu\text{g}/\text{m}^3$ and $< 2 \mu\text{g}/\text{m}^3$ for the two worst processes (Sprince et al., 1978). Hypoxemia was significantly decreased in the 13 hypoxemic workers who were available for follow-up, and 9 of the workers with initial evidence of interstitial lung disease had normal chest radiographs. This study suggests that early clinical signs of CBD can be reversed by reduced exposure to beryllium. However, because neither beryllium sensitization nor CBD were shown in the workers exposed between 1971 and 1974, the strength of this conclusion is weakened.

In a cross-sectional study of 297 white male workers at a beryllium extraction facility, Kriebel et al. (1988b) analyzed the following pulmonary function parameters: forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), maximum mid-expiratory flow (MMEF), and alveolar-arterial oxygen gradient (AaDO_2). Exposure data using area samplers and/or personal sampling were available from 1947 and later. Individual exposure was estimated on the basis of reported job titles and exposure at each job during different periods (Kriebel et al., 1988a). Exposure decreased dramatically during the period of assessment; average exposures at dirty jobs were above 25 $\mu\text{g}/\text{m}^3$ prior to the 1960s. The median cumulative exposure was 65 $\mu\text{g}/\text{m}^3\text{-year}$, and the median of the mean lifetime exposures was 4.3 $\mu\text{g}/\text{m}^3$. Both exposures to beryllium fumes and to beryllium or beryllium oxide dust occurred. Correlations between pulmonary function parameters and exposure were determined, but no attempt was made to separately identify workers with CBD. A significant ($p < 0.05$) correlation was observed between decreased FVC and FEV_1 and exposure for ≥ 21 years. There was also a significant correlation

between cumulative exposure and increased (worse) AaDO₂ values, but not with other pulmonary function parameters. Mild radiological abnormalities were seen in some workers. The absence of more severe findings can probably be attributed to the healthy worker effect. Labor turnover in the plant was very high during the years when exposure was high, and the sensitive workers had probably left because of acute beryllium disease or CBD. Because workers were not grouped by exposure level, the data are insufficient to determine levels at which such effects are seen. In addition, because those with CBD were not separately identified, the magnitude of the exposure-response relationship was probably decreased.

In a 3-year prospective study of beryllium mine and mill workers, Rom et al. (1983) found that beryllium sensitization, based on blastogenic lymphocyte transformation (LT), was reversible when exposure levels decreased. In the initial assessment of 197 workers, there were 15.9% (13/82) positives (LTs), based on the peripheral blood BeLT; 8.2% (5/61) were positive in the follow-up of 1982. Of 11 of the 13 workers who were positive (LTs) initially and were tested in the follow-up study, 8 had lost their sensitivity at the second test. In the baseline year, one-third of the beryllium monitoring samples exceeded 2 µg/m³, and the mean exposure level was 7.18 µg/m³. By contrast, only 11% of the samples exceeded 2 µg/m³ in the following 3 years, and the average was 0.25, 0.40, and 0.99 µg/m³ in successive years. Only qualitative individual exposure levels were reported. Most of the sensitized individuals had higher exposure levels, but cases of sensitization were also reported in people with low exposure. A positive BeLT result was not associated with decreased respiratory function. None of the study participants developed CBD. Although the study authors presented some data on reproducibility of results, their assay does not appear to be as sensitive or reproducible as later versions of this assay (e.g., Mroz et al., 1991), and the apparent reversibility may have been due to false positives in the initial assay or false negatives in the repeat assay.

Acute chemical pneumonitis resulting from high-level beryllium exposure has also been reported. Acute beryllium disease is defined as beryllium-induced pulmonary disease with less than a year's duration (Sprince and Kazemi, 1980). Acute beryllium lung disease is likely to be due to direct toxicity, unlike the immune mechanism of CBD. As of 1977, there were 887 cases in the beryllium case registry. Of these, 631 were classified as chronic, 212 as acute, and 44 as acute developing to CBD. Thus, early cases of CBD sometimes also had acute beryllium disease. Due to the markedly decreased levels of occupational exposure to beryllium, acute chemical pneumonitis is now quite rare. Only one acute case was added to the registry in 1972-75, but there was about one case of CBD per month during the same period (Sprince and Kazemi, 1980).

CBD has resulted in death, especially prior to the implementation of more rigid controls in 1949, when exposure was much higher than it is now. In a cohort mortality study of 689 patients with CBD who were included in the case registry, there was a high rate of deaths due to pneumoconiosis, primarily CBD (Standardized Mortality Ratio [SMR] = 34.23, 95% confidence interval of 29.1-40.0, 158 deaths) (Steenland and Ward, 1991). Similar results (SMR = 1640, $p < 0.05$, 52 deaths) were observed in an earlier analysis of deaths in the beryllium case registry due to nonneoplastic respiratory disease (Infante et al., 1980). Deaths have also been reported in community cases of CBD, including a 10-year-old girl (Lieben and Williams, 1969). Some of these cases have been confirmed based on histological evidence of CBD and evidence of beryllium in the lungs.

4.1.2. Lung Cancer

A number of cohort mortality studies have investigated the carcinogenic potential of beryllium in beryllium processing workers employed in seven facilities in the United States. Several studies published in 1971, 1979, and 1980 were critically reviewed in U.S. EPA (1987b). A brief description of these studies, as well as a discussion of the major criticisms, is included in this section. Two new studies (Ward et al., 1992; Steenland and Ward, 1991) not previously reviewed by EPA are also discussed in this section. MacMahon (1994), in a review funded by the Beryllium Industry Scientific Advisory Committee (BISAC), cited serious defects in the methodology of the early (pre-1987) epidemiologic studies that linked occupational beryllium exposure to lung cancer, and questioned the interpretation of the more recent, and generally better grounded, epidemiologic studies (Steenland and Ward, 1991; Ward et al., 1992) that IARC reviewed in 1993.

The Ward et al. (1992) study of the seven beryllium producing plants in Ohio and Pennsylvania is basically an update of several earlier retrospective cohort studies (Bayliss et al., 1971; Mancuso, 1979, 1980; Wagoner et al., 1980). Since these studies are follow-up studies and not independent of each other, they will be discussed in chronological sequence.

Bayliss et al. (1971) studied $\approx 7,000$ past and current workers (out of 10,356) in the beryllium processing industry in Ohio and Pennsylvania. They observed a slightly elevated risk of lung cancer (36 observed versus 34.06 expected), but the results were not statistically significant. The report does not specify the plants but implies, as does MacMahon (1994), that all the beryllium processing facilities were included. Limitations of this study include the elimination of $> 2,000$ workers because of incomplete data, lack of analysis of the data according to length of time since initial employment, and the combining of populations from several different plants into one cohort (U.S. EPA, 1987b). Follow-up studies conducted by Mancuso (1979, 1980) and Wagoner et al. (1980) focused on cohorts from only one or two of the plants.

Mancuso (1979) examined lung cancer mortality in two cohorts of beryllium workers employed between 1942 and 1948 and followed through 1974 and 1975 for Ohio and Pennsylvania, respectively. The first cohort (1,222 workers, 888 alive and 334 dead) comprised workers at an Ohio facility. The second cohort comprised 2,044 workers (1,257 alive and 787 dead) at a Pennsylvania facility. Lung cancer mortality (also includes deaths from trachea and bronchus cancer) was compared to mortality in the U.S. white male population (using vital statistics data for the period ending in 1967). In both cohorts, significant ($p < 0.05$) increases in the total number of lung cancer deaths were observed (SMR = 2.07 and 1.52 for the Ohio and Pennsylvania cohorts, respectively). Dividing workers into groups based on employment duration and latency period (interval since onset of employment) resulted in significant increases in lung cancer mortality in workers employed at the Ohio (SMR = 2.31) and Pennsylvania (SMR = 1.82) facilities for < 5 years with a latency of ≥ 15 years, but not in workers with a longer employment duration or shorter latency. As with the Wagoner et al. (1980) study, discussed subsequently in this section, using U.S. white male lung cancer mortality rates for the period ending in 1967 to estimate expected cases for 1968-1975 resulted in a 10% to 11% underestimation of expected lung cancers because nationwide lung cancer rates were increasing. A serious omission of this study is the lack of discussion of the potential confounding effect of cigarette smoking on lung

cancer mortality. Because the Pennsylvania cohort used in this study was drawn from the same beryllium plant as the cohort in the Wagoner et al. (1980) study, it is likely that the beryllium cohort had a higher percentage of smokers than the comparison population. Smoking data were not available for the Ohio cohort.

In the Mancuso (1980) study, the beryllium-exposed cohort comprised 3,685 workers (2,329 alive and 1,356 dead) employed at the Ohio and Pennsylvania beryllium production facilities between 1937 and 1948. The comparison group consisted of 5,929 workers, 4,105 alive and 1,824 employed at a viscose rayon plant from 1938 to 1948. A limited description of the comparison group was provided. Both groups of workers were followed to the end of 1976. Lung cancer mortality for the beryllium cohort was compared to the mortality rates for the entire viscose rayon industry worker cohort and to a subset of workers who did not transfer between departments during their employment in the viscose rayon industry. The rationale for having the two comparison groups was not stated. A significant ($p < 0.05$) increase in lung cancer mortality was observed in the beryllium cohort, as compared to the entire rayon cohort (SMR = 1.40) and to those never transferring to a different department (SMR = 1.58). When the cohorts were divided by duration of employment, a significant increase in lung cancer deaths was observed in beryllium workers employed for < 1 year (SMR = 1.38 and 1.64 compared to the entire rayon cohort and those not transferring departments) and > 4 years (SMR = 2.22 and 1.72), but not in workers employed for > 1 year and ≤ 4 years. The effect of latency was not assessed. As with the Mancuso (1979) study, a serious limitation of this study is the lack of control of the confounding factor of cigarette smoking. EPA (1987b) questioned whether Mancuso adjusted for age differences between the beryllium cohort and the viscose rayon cohort. Additionally, EPA (1987b) notes that NIOSH re-analyzed the data from this study and found "serious problems with Mancuso's analysis." No additional information was available to EPA.

A cohort mortality study of 3,055 white males employed between 1942 and 1967 at a beryllium extraction, processing, and fabrication facility in Reading, PA, was conducted by Wagoner et al. (1980). The study cohort was followed through 1975. The total number of deaths (875) was not significantly different from the number expected on the basis of age and calendar time period for the general white male U.S. population (vital statistics data for the period 1965-1967 were assumed to be those of 1968-1975). Significant ($p < 0.05$) increases in the number of deaths due to malignant neoplasm of trachea, bronchus, and lung (47 deaths observed versus 34.29 expected, SMR = 1.37), heart disease (SMR = 1.13), and nonneoplastic respiratory disease (excluding influenza and pneumonia) (SMR = 1.65) were observed in the study cohort. When deaths from lung cancer were segregated by latency (interval since onset of employment) and duration of employment, significant increases were observed for workers with a ≥ 25 -year latency employed for < 5 years (17 observed versus 9.07 expected, SMR = 1.87) and across all employment durations (20 observed versus 10.79 expected, SMR = 1.87). (It should be noted that 83% of the cohort was employed for < 5 years.) When lung cancer mortalities were partitioned based on initial date of employment, lung cancer deaths were significantly higher in workers hired before 1950 (SMR = 1.35; $p < 0.05$); an increase in deaths in workers hired after 1950 was also found, but it was not statistically significant (SMR = 1.52). (Prior to 1950, beryllium exposures were not controlled, and it is likely that the workers were exposed to high concentrations of beryllium.) Similar findings were reported when nonneoplastic respiratory disease mortalities were segregated; a significant increase in mortality was observed in the

workers in the ≥ 25 -year latency and < 5 -year employment category (SMR = 2.13). In the workers who were hired prior to 1950, a significant increase in mortality from nonneoplastic respiratory disease was observed (SMR = 1.85). This was not observed for workers whose initial date of employment was after 1950 (0 deaths observed versus 2.03 expected). Wagoner et al. (1980) noted that using U.S. population data rather than county mortality data resulted in an overestimation of expected lung cancer deaths by a factor of 19% (and thus a corresponding underestimation of lung cancer risk for the cohort) because residents of Berks County (where most of the workers lived) have a lower lung cancer rate (31.8 per 100,000) than the U.S. population (38.0 per 100,000). The percentage of beryllium workers living in the city of Reading, however, was higher than for county residents in general, and higher lung cancer rates are observed in urban residents as compared to residents living in rural areas. EPA (1987b) estimated that comparing lung cancer mortality in the beryllium cohort to county rates weighted toward the city of Reading rates, which were 12% higher than the national rates, would result in an increased number of expected deaths. It is generally preferable to use county data, although the issue of urban residence may dictate using general U.S. data if the cohort is more urban- oriented.

Wagoner et al. (1980) compared cigarette smoking histories of the cohort and the U.S. population using smoking habit information collected during a medical survey in 1968 and cigarette smoking data for white males from a Public Health Service Survey conducted in 1964-1965. A smaller percentage of the cohort were current smokers (49.6% never smoked or were former smokers versus 45.2% in the U.S. population), but the percentage of current smokers smoking more than one pack per day was higher (21.4% versus 15.3%). The investigators estimated that not adjusting lung cancer incidence data for differences in cigarette smoking habits resulted in an overestimation of lung cancer risks by a factor of 14%.

This study has severe limitations, including the following:

1. The use of U.S. white male mortality data for the period of 1941 to 1967, which resulted in an underestimation of the number of expected lung cancer deaths because lung cancer death rates in the United States were increasing during the period 1968-1975. The expected number of lung cancer deaths should have been 10%-11% higher (U.S. EPA, 1987b; Saracci, 1985).
2. The inclusion of one lung cancer death of an individual who was paid for the pre-employment physical but was not hired (U.S. EPA, 1987b).
3. The exclusion of approximately 300 white males employed at the Reading facility in similar jobs as the workers included in the cohort (U.S. EPA, 1987b).
4. The inadequate discussion of confounding effects from other potential lung carcinogens (U.S. EPA, 1987b).

The above limitations of the study tended to exaggerate the risk of lung cancer in this population of workers potentially exposed to beryllium (MacMahon, 1994; U.S. EPA, 1987b).

EPA (1987b) adjusted the lung cancer SMRs from the Wagoner et al. (1980) study. The expected lung cancer deaths were increased by 11% to account for the underestimation that occurred from using older vital statistics and by 4.1% to account for differences in smoking habits between the beryllium cohort and the U.S. population. The one ineligible lung cancer death was removed from the observed deaths. Although the SMRs for latency ≥ 25 years remained elevated after this adjustment, they were no longer statistically significant (Table 3).

Ward et al. (1992) conducted a retrospective cohort mortality study of 9,225 men (5,681 alive and 3,240 dead) employed for at least 2 days between January 1, 1940, and December 31, 1969, and followed through December 31, 1988, at any one of seven beryllium processing facilities located in Reading, PA, Hazelton, PA, Lorain, OH, Cleveland, OH (data for Perkins and St. Clair plants combined), Lucky, OH, and Elmore, OH. Cohort members were identified from quarterly earning reports from the Social Security Administration and compared to personnel files. Workers identified from quarterly earning reports without personnel files were only included in the cohort if they appeared on at least two quarterly earning reports. Workers who worked at more than one facility were placed into a seventh category termed "multiple plant." Vital statistics for the workers were obtained from the Social Security Administration, Internal Revenue Service, post office cards mailed to the last known address, Veterans Administration, Health Care Financing Administration, and the National Death Index. Vital statistics were not located for 304 (3.3%) individuals, and death certificates were not obtained for 46 (0.4%) individuals known to be deceased.

The workers at the beryllium processing facilities were involved in the extraction of beryllium hydroxide from beryl ore; the production of beryllium oxide, pure beryllium metal, and beryllium copper alloy; and the machining of beryllium-containing products. The beryllium compounds the workers were potentially exposed to include beryllium sulfate mists and fumes, beryllium oxide dusts, beryllium ammonium fluoride and beryllium fluoride dusts, beryllium metal, and beryllium copper alloy dusts and fumes. In addition to exposure to beryllium, the workers were also potentially exposed to ore dust, silicon dioxide fumes, lead sulfide, copper sulfide, sulfur trioxide, acid fluoride mists, hydrogen fluoride, and ammonium fluoride. In addition, according to BISAC (1997), exposure to sulfuric acid mists and fumes occurred in the Lorain facility. Because no occupational history data other than starting and ending dates of employment were coded, and no individual monitoring data were available, the study could not address the relationship of degree of beryllium exposure or type of beryllium compound to lung cancer risk. Ward et al. (1992) noted that prior to 1949, when controls were not mandated, air concentrations of beryllium were very high, frequently exceeding $1,000 \mu\text{g}/\text{m}^3$.

When mortality from all causes in the entire cohort was compared to mortality rates from the U.S. population, a significant ($p < 0.05$) increase in risk was observed (SMR of 1.05, 95% confidence interval [CI] of 1.01-1.08). Excess deaths were also observed for malignant neoplasm of the trachea, bronchus, and lung (SMR = 1.26, 95% CI = 1.12-1.42), ischemic heart disease (SMR = 1.08, 95% CI = 1.01-1.14), pneumoconiosis and other respiratory disease (SMR = 1.48, 95% CI = 1.21-1.80), and chronic and unspecified nephritis, renal failure, and other

Table 3. Observed and expected deaths due to lung cancer in beryllium processing facility workers

| Interval since onset of employment | Duration of employment ^{a,b} | | | | | | | | |
|------------------------------------|---------------------------------------|-------|------|-----------|------|------|-------|-------|------|
| | < 5 years | | | > 5 years | | | Total | | |
| | O | E | SMR | O | E | SMR | O | E | SMR |
| < 15 years | 7 | 8.88 | 0.79 | 1 | 1.76 | 0.57 | 8 | 10.64 | 0.75 |
| 15-24 years | 15 | 13.44 | 1.12 | 3 | 3.15 | 0.95 | 18 | 16.59 | 1.08 |
| ≥ 25 years | 17 | 12.00 | 1.42 | 3 | 2.67 | 1.12 | 20 | 14.67 | 1.36 |
| Total | 39 | 34.32 | 1.14 | 7 | 7.58 | 0.92 | 46 | 41.90 | 1.10 |

^aWorkers employed during 1942 through 1967 and followed through 1975.

^bNo comparisons were statistically significant at $p < 0.05$.

O = observed deaths; E = expected deaths; SMR = standardized mortality ratio.

Source: modified from Wagoner et al., 1980, by U.S. EPA, 1987b.

renal sclerosis (SMR = 1.49, 95% CI = 1.00-2.12). Examination of the cause of death on a per-plant basis revealed that only the Lorain and Reading facilities (the two oldest plants) had significant excesses in lung cancer: total SMRs of 1.69 and 1.24, respectively. In addition, the Cleveland and Hazelton facilities had nonsignificant excesses in lung cancer (total SMRs > 1). Data on lung cancer deaths for the whole cohort and for each plant are presented in Table 4.

A significant excess of pneumoconiosis and other respiratory disease was also observed at the Lorain facility (SMR = 1.94). Increased employment duration was not associated with an increase in lung cancer SMR; when lung cancer mortalities were stratified by employment duration category, the only significant increase in lung cancer SMRs was for workers employed < 1 year. However, there was a tendency for lung cancer SMRs to increase with increasing latency; SMRs were statistically significantly elevated in the > 30-year latency category for all employment durations combined (SMR = 1.46) and for workers employed for < 1 year (SMR = 1.52), and in the 25- to 30-year latency category for workers employed for < 1 year. Additionally, decade of hire influenced lung cancer mortality. The SMR (1.42) was statistically elevated in workers hired before 1950; this was mainly influenced by mortality in the Lorain plant, which closed in 1948. Of the two other facilities in operation before 1950 (Reading and Cleveland), an increased lung cancer rate was found at the Reading facility (SMR = 1.26 for workers hired before 1950). With the exception of those hired before 1950 (total SMR = 1.42), no other significant increases in lung cancer deaths were observed when workers were grouped by decade of hire. Nonsignificant increases were seen for the 1950s decade at the Reading (SMR = 1.42), Cleveland (SMR = 1.32), Elmore (SMR = 1.42), and Hazelton (SMR = 1.86) facilities. Regression analysis (controlling for age, race, and calendar period of risk) showed that decade of hire was independent of potential latency (time since first employment).

Table 4. Lung cancer mortality in male beryllium workers employed between 1940 and 1969 and followed through 1988 by facility worked and latency (time since first employment)

| Facility | Latency < 15 years | | | Latency 15-30 years | | | Latency > 30 years | | | Total | | |
|-----------------|-----------------------|------|------|------------------------|------|-------------------|-----------------------|------|-------------------|-------|-------|-------------------|
| | Obs. | Exp. | SMR | Obs. | Exp. | SMR | Obs. | Exp. | SMR | Obs. | Exp. | SMR |
| Lorain | 1 | 2.6 | 0.38 | 21 | 10.0 | 2.09 ^a | 35 | 21.1 | 1.66 ^b | 57 | 33.8 | 1.69 ^b |
| Reading | 9 | 11.5 | 0.78 | 44 | 37.5 | 1.17 | 67 | 47.9 | 1.40 ^b | 120 | 96.9 | 1.24 ^b |
| Lucky | 1 | 1.0 | 0.96 | 4 | 4.7 | 0.85 | 4 | 5.3 | 0.76 | 9 | 11.0 | 0.82 |
| Cleveland | 9 | 6.9 | 1.30 | 20 | 22.0 | 0.91 | 15 | 11.8 | 1.27 | 44 | 40.7 | 1.08 |
| Elmore | 2 | 3.9 | 0.51 | 12 | 10.5 | 1.14 | 1 | 0.8 | 1.31 | 15 | 15.2 | 0.99 |
| Hazelton | 4 | 2.1 | 1.91 | 9 | 7.1 | 1.26 | 0 | 0.2 | - | 13 | 9.4 | 1.39 |
| Multiple plants | 0 | 0.7 | - | 4 | 3.2 | 1.23 | 9 | 3.8 | 2.38 | 13 | 7.6 | 1.67 |
| Unknown | 1 | 1.6 | 0.64 | 5 | 3.9 | 1.28 | 3 | 1.3 | 2.30 | 9 | 6.8 | 1.33 |
| Total | 27 | 30.3 | 0.89 | 119 | 99.1 | 1.20 ^b | 134 | 92.1 | 1.46 ^a | 280 | 221.5 | 1.26 ^a |

^aTwo-sided, $p < 0.01$.

^bTwo-sided, $p < 0.05$.

SMRs not adjusted for differences in smoking habits between exposed cohort and U.S. population.

Source: Ward et al., 1992.

The influence of geographic variation in lung cancer mortality was evaluated, comparing lung cancer mortality found in the beryllium cohort to lung cancer rates for the cohort where most of the workers resided. Lung cancer mortality was significantly elevated in workers at the Lorain (SMR = 1.60, 95% CI = 1.21-2.08) and Reading (SMR = 1.42, 95% CI = 1.18-1.69) facilities as compared to residents of Lorain County and Berks County, respectively. The investigators noted that county residents may not serve as a better referent group than the U.S. population because the percentage of workers at the Lorain and Reading facilities residing in an urban area was approximately 3 times higher than the percentage of county residents living in urban areas.

Data on the smoking habits of the entire beryllium cohort were not available. Some information was available from a 1968 Public Health Service survey conducted at the Reading, Hazelton, Elmore, and St. Clair facilities (it included 15.9% of the cohort members). These data were compared to smoking habits of the U.S. population obtained from averaging smoking surveys conducted in 1965 (National Center for Health Statistics) and 1970 (Office of Health Research, Statistics, and Technology). A comparison of the SMRs for malignant neoplasms of the trachea, bronchus, and lung using county and U.S. rates is presented in Table 5. The estimated relative risk ratio for lung cancer for the beryllium cohort to the U.S. population was calculated using estimated risks of 1 for nonsmokers, 6.5 for current smokers of ≤ 1 pack per day, 13.8 for smokers of > 1 pack per day, and 6.2 for former smokers. The relative risk ratio or smoking adjustment was 1.1323, which indicates that smoking alone could account for an SMR of 1.13.

Using the smoking adjustment factor, smoking-adjusted SMRs were calculated for the entire cohort and the Lorain and Reading facilities. The resultant SMRs were 1.12, 1.49, and 1.09, respectively. An additional analysis of the data from the Ward et al. (1992) study by BISAC (1997) shows SMRs and CI estimates, before and after adjustment for smoking, for the two older plants that contributed the larger number of lung cancer cases, for the newer plants taken together, and for the total cohort (Table 6). One process exposure, to which BISAC (1997) attributed the excess cancer (SMR 1.49) after adjustment for smoking, and which was briefly mentioned by Ward et al. (1992), is exposure to mists and vapors from sulfuric acid and the related sulfur oxide gases. Such exposure, according to BISAC (1997), was very high in the Lorain plant. This was the only plant that used a sulfuric acid-dependent process with limited ventilation (Kjellgren, 1946); at the time, the occupational inhalation risks associated with airborne beryllium (acute pneumonitis) and airborne sulfuric acid (respiratory cancer) had not yet been established. Because the 1968 survey data are the only information available on the smoking habits of the beryllium cohort, an assumption was made that the smoking habit difference between the cohort and the U.S. population found in the late 1960s was the same in the 1940s and 1950s. Other investigators have shown that increased smoking is unlikely to account for SMRs greater than 1.3 for lung cancer and other smoking-related diseases (Siemiatycki et al., 1988).

Ward et al. (1992) examined the BCR mortality study file to determine how many of the members of the cohort were registered (i.e., had a history of beryllium disease). The Lorain plant had the highest percentage of registrants: 8.2% (98 of 1,192 workers); 93% of these were listed

Table 5. SMRs for malignant neoplasm of the trachea, bronchus, and lung among U.S. male beryllium workers employed 1940-1969 and followed through December 31, 1988, using county death rates (1950-1983) for comparison

| Plant location | | Obs. | SMR based on county rates | 95% CI | SMR based on U.S. rates |
|------------------------|--------------|----------------|---------------------------|-----------|-------------------------|
| City | County | | | | |
| Lorain | Lorain, OH | 57 | 1.60 ^a | 1.21-2.08 | 1.69 ^a |
| Reading | Berks, PA | 120 | 1.42 ^a | 1.18-1.69 | 1.24 ^b |
| Lucky | Ottawa, OH | 9 | 0.84 | 0.38-1.59 | 0.82 |
| | Sandusky, OH | - ^c | - | - | - |
| | Wood, OH | - | - | - | - |
| Cleveland ^d | Cuyahoga, OH | 44 | 1.05 | 0.76-1.41 | 1.08 |
| Elmore | Ottawa, OH | 15 | 1.06 | 0.59-1.75 | 0.99 |
| | Sandusky, OH | - | - | - | - |
| | Wood, OH | - | - | - | - |
| Hazleton | Carbon, PA | 13 | 1.50 | 0.80-2.57 | 1.39 |
| Sum of 6 locations | | 258 | 1.32 ^{b,c} | 1.19-1.46 | 1.26 ^{a,c} |

^aTwo-sided *p*-value less than 0.01.

^bTwo-sided *p*-value less than 0.05.

^c- = No data.

^dSt. Clair and Perkins combined.

^eTotal study population (n = 9,225, 280 lung cancer); six locations population (n = 8,672, 258 lung cancer).

Source: Ward et al., 1992.

Table 6. Observed and expected lung cancer cases, before and after external adjustment for differences in smoking habits between exposed cohorts and U.S. population, and corresponding standardized mortality ratios (SMRs) with 95% confidence intervals (CI), workers from Lorain, Reading, and all other plants

| Plant | Lung cancer observed cases | No adjustment for smoking | | | Adjustment for smoking | | |
|------------|-------------------------------|---------------------------|---------------------|---------|------------------------|---------------------|---------|
| | | Expected cases | SMR (CI) | P-value | Expected cases | SMR (CI) | P-value |
| Lorain | 57 | 33.8 | 1.69 (1.28-2.19) | 0.0003 | 38.2 | 1.49 (1.13-1.93) | 0.005 |
| Reading | 120 | 96.9 | 1.24 (1.03-1.48) | 0.026 | 109.8 | 1.09 (0.91-1.31) | 0.353 |
| All others | 103 | 90.8 | 1.13 (0.93-1.38) | 0.222 | 102.8 | 1.00 (0.82-1.22) | 0.990 |
| Total | 280 | 221.5 | 1.26 (1.12-1.42) | 0.0002 | 250.8 | 1.12 (0.99-1.26) | 0.074 |

Source: BISAC, 1997, from data of Ward et al., 1992.

as having had acute beryllium disease, which is associated with very high exposure (Eisenbud and Lisson, 1983). The lung cancer SMR for the Lorain workers in the BCR was 3.33 (95% CI = 1.66-5.95), compared to 1.51 (95% CI = 1.11-2.02) for the remaining Lorain workers.

Ward et al. (1992) concluded that a plausible explanation for the increased lung cancer rates is occupational exposure to beryllium. Although the results of this study are suggestive that occupational exposure to beryllium can result in an increase in lung cancer mortality, interpretation of this study is limited by a number of factors:

1. No data (including job history data) were available to associate beryllium exposure levels, exposure to specific beryllium compounds, or concomitant exposure to other chemicals with members of the cohort.
2. Because of the lack of job history data, it is possible that the cohort contained salaried workers and other nonproduction personnel who may not have been exposed to beryllium.
3. The limitations in the available smoking habit data, as discussed above, may have led to an over- or underestimation of the contribution of smoking to the lung cancer rates.
4. A large percentage (73.1%) of the workers were employed in the beryllium industry for ≤ 5 years. This is particularly true at the Lorain facility, where 84.6% of the workers were employed for < 1 year. EPA (1987b) points out that there is a possibility that the workers were exposed to other potential carcinogens at jobs held before or after the beryllium job; the two facilities with the highest cancer rates (Lorain and Reading) are located in or near heavily industrialized areas.

Formal epidemiological studies of BCR enrollees have been undertaken to assess the long-term mortality patterns, and particularly carcinogenic risk, among a beryllium-exposed population. The first of these studies included all white males alive at the time of entry into the BCR, with follow-up through 1975 (Infante et al., 1980); the second included all cases, regardless of sex or race, alive at the time of entry into the registry through 1988 (Steenland and Ward, 1991). Thus, these studies differ from the investigation of Ward et al. (1992), which assessed only those BCR registrants who also were members of the cohort of beryllium processing workers in their retrospective cohort study.

Infante et al. (1980) examined the possible relationship between beryllium exposure and lung cancer in a cohort mortality study of 421 white males entered into the BCR between July 1952 and December 1975 with the diagnosis of beryllium disease. The cohort did not include subjects who were deceased at the time of BCR entry. No information on occupations was provided in the report, but IARC (1993), in its review of this study, mentioned that the majority of individuals in the BCR worked in beryllium extraction and smelting, metal production, and fluorescent tube production, and a small number were not exposed occupationally but lived near the plants. Cause-specific mortality data from the U.S. population for the period of 1965-1967

(matched for race, sex, age, and calendar time period) were used for comparisons. A significant ($p < 0.05$) increase in deaths from cancer was observed (SMR = 1.53), but the number of lung cancer deaths (includes cancer of the trachea, bronchus, and lung) (7 observed vs. 3.3 expected, SMR = 2.11) was not significantly increased. A significant increase in nonmalignant respiratory disease (excludes influenza and pneumonia) mortality was observed (SMR = 32.1). Cancer mortalities were segregated into workers with a diagnosis of acute beryllium-related respiratory illness ($n = 223$) and those with chronic beryllium-related diseases ($n = 198$). Acute beryllium disease was defined as a diagnosis of chemical bronchitis, pneumonitis, or other acute respiratory illness at the time of entry into the registry. Chronic beryllium disease was defined as a diagnosis of pulmonary fibrosis or some recognized chronic lung condition at the time of entry into the registry. For subjects without a clear diagnosis, categorization was based on the interval between initial exposure and first respiratory symptoms (within 1 year of initial exposure was considered acute). Significant increases in deaths from lung cancer were observed in the acute beryllium illness group (SMR = 3.14). Most of these deaths were observed in workers with > 15 -year latencies (SMR = 3.21). Deaths from lung cancer were not elevated in the group with chronic respiratory illness (SMR = 0.72). The authors note that this may be due to the high case-fatality rate for nonneoplastic respiratory disease in the workers with chronic beryllium illnesses. Significant increases in deaths from nonneoplastic respiratory disease were observed in the group with acute beryllium illness (SMR = 10.3) and in the chronic beryllium illness group (SMR = 64.6). The lung cancer mortality rates were not adjusted for cigarette smoking because smoking habit information was not obtained from the cohort. The investigators noted that it was highly unlikely that workers with acute beryllium illnesses had smoking habits of sufficient magnitude to account for the excessive lung cancer risk observed in that group. As with the Wagoner et al. (1980) and Mancuso (1980) studies, using U.S. mortality rates for the period ending in 1967 probably resulted in an underestimation of expected lung cancer deaths. It is likely that this distortion was similar to the one found in the Wagoner et al. (1980) study (11%). On the other hand, Steenland and Ward's (1991) analysis of smoking habit information as of 1965 for their cohort from the BCR (see below) indicated that not correcting for differences in smoking habits between the cohort and the U.S. population may overestimate the expected deaths.

Steenland and Ward (1991) extended this earlier study of BCR enrollees by including females and by adding 13 years of follow-up. Cancer mortality was examined in a cohort of 689 males and females (66% of the cohort was male; 261 alive and 428 dead) who were entered in the BCR. All members of the cohort were alive at the time of entry and were followed until the time of death or until 1988. Among the cohort members, CBD (64%; 50% in males and 91% in females) was more common than acute disease. The members had worked in the fluorescent tube industry (34%) or basic manufacturing (36%), or were members of a community exposed to high beryllium levels (6%), or their records lacked industry/exposure scenario information (10%). Mortality rates for the cohort were compared with the U.S. population (stratified by age, race, sex, and calendar time). Smoking habit information as of 1965 was available for 32% of the cohort (obtained from direct interviews, interviews with next of kin, or registry records). This information was compared to smoking habits of the U.S. population as of 1965. The SMR for lung cancer mortality was increased for the total cohort (2.00, 95% CI = 1.33-2.89), for males (1.76, 95% CI = 1.02-2.67), and for females (4.04, 95% CI = 1.47-8.81). When the cohort was divided into groups based on duration of beryllium exposure (≤ 4 years and > 4 years) and time since first exposure (≤ 20 years and > 20 years), significant trends in lung cancer rates were not

observed. However, the authors noted that the duration of exposure information in the registry was likely to contain a number of inaccuracies. An increased SMR was also observed for pneumoconiosis and other respiratory diseases (26.30, 95% CI = 20.6-33.1); the SMR for the group exposed to beryllium for > 4 years (45.78, 95% CI = 36.6-56.5) was significantly ($p < 0.001$) higher than for the group exposed ≤ 4 years (26.30, 95% CI = 20.6-33.1). Dividing the cohort based on whether they were diagnosed with acute or chronic beryllium disease revealed a higher lung cancer SMR for workers in the acute disease group (presumably they were exposed to higher levels of beryllium; SMR = 2.32, 95% CI = 1.35-3.72) than in the chronic disease group (SMR = 1.57, 95% CI = 0.75-2.89). The SMR for pneumoconiosis and other respiratory diseases was higher in the chronic disease group (68.64, 95% CI = 57.8-81.0) than in the acute disease group (SMR = 6.55, 95% CI = 3.74-10.6). The smoking habits of 32% of the cohort were available from direct interviews, interviews with next of kin, or registry records. The cohort smoking habits as of 1965 were compared to U.S. population smoking habits as of 1965. The authors note that 1965 was chosen as a time point "because smoking habits in the 1960s are considered to have been most relevant for lung cancer mortality in the 1980s." The cohort contained fewer current smokers and more former smokers than the comparison U.S. population, perhaps because the presence of respiratory disease in this cohort deterred smoking. Taking into account the known relative risks for various smoking habit categories for the cohort as compared with the U.S. population, the SMR for the cohort based on smoking alone was 0.98 for men and 0.86 for women. The investigators concluded that if the smoking habits of the entire cohort were represented by the 32% with smoking habit data, then it "would be unlikely that smoking was a cause of the observed lung cancer excess." Other studies (Ward et al., 1992; Wagoner et al., 1980) found that not correcting for differences in cigarette smoking-related lung cancer deaths between the exposed cohort and comparison population would result in an underestimation of expected deaths, which differs from the conclusions of Steenland and Ward (1991).

4.2. PRECHRONIC AND CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS—ORAL AND INHALATION

4.2.1. Oral Exposure

In a chronic toxicity study by Morgareidge et al. (1975, 1977), groups of Wistar albino rats were fed diets containing 5, 50, or 500 ppm beryllium as beryllium sulfate tetrahydrate. The rats were administered the beryllium-containing diet from 4 weeks of age through maturation, mating, gestation, and lactation. Fifty male and 50 female offspring were then placed on the same diets as the parents and fed the beryllium-containing diet for 104 weeks. Using estimated TWA body weights of 0.467, 0.478, and 0.448 kg for males in the 5, 50, and 500 ppm groups and 0.294, 0.302, and 0.280 kg for the females, respectively, and EPA's (1988) allometric equation of food intake, doses of 0.36, 3.6, and 37 mg/kg-day for males in the 5, 50, and 500 ppm groups and 0.42, 4.2, and 43 mg/kg-day for females in the 5, 50, and 500 ppm groups, respectively, were calculated. Clinical observations, body weight, food consumption, organ weights (liver, kidney, testes, ovaries, thyroid, pituitary, adrenal), gross necropsy, and histopathological examination of most tissues and organs (25-26 tissues examined) were used to assess the toxicity and carcinogenicity of beryllium in the offspring; it does not appear that the P_0 rats were examined. Tissues from 20 rats/sex/group in the control and 500 ppm groups were examined microscopically

(the study authors did not state whether the animals undergoing histopathological examination were randomly selected), as well as all tissues with gross abnormalities (all groups) and tissues (excluding bone marrow, eyes, and skin) from animals found dead or sacrificed moribund (all groups).

No overt signs of toxicity were observed, and mortality appeared to be similar in the controls (30/50 males and 28/50 females died) and beryllium groups at 5 ppm (30/50 and 24/50, respectively), 50 ppm (31/50 and 18/50), and 500 ppm (24/50 and 17/50) at the end of the 104 weeks of the study. During the first 40-50 weeks of the study, exposure to beryllium did not appear to affect growth. Slight decreases in growth (body weights of males and females in the 500 ppm group were within 10% of control body weights) were observed in the latter part of the study; however, no statistically significant alterations were observed. Alterations in organ weights were limited to statistically significant ($p < 0.05$) increases in relative kidney weight in males exposed to 50 ppm, decreases in relative kidney and adrenal weights in 500 ppm females, and decreases in relative testes weights in 5 and 50 ppm males. Histological examination of the major organs and tissues did not reveal beryllium-related noncarcinogenic alterations. These data suggest that the maximum tolerated dose (MTD) was not reached.

Reticulum cell sarcomas were observed in a number of tissues examined, including the lungs, lymph nodes, spleen, liver, kidneys, and pancreas; the highest incidence was in the lungs. Because lymphomas (reticulum cell sarcoma is a type of lymphoma) are almost always detected grossly, reticulum cell sarcoma incidences were calculated based on the number of tissues grossly examined (all gross diagnoses were confirmed histopathologically) rather than on the number of tissues microscopically examined. In most organs, the incidence of reticulum cell sarcomas was not significantly higher in the beryllium-exposed rats, as compared to controls. In the lung, the incidences of reticulum cell sarcoma were 10/50, 17/50, 16/50, and 12/50 in males and 5/50, 7/50, 7/50, and 5/50 in females exposed to 0, 5, 50, or 500 ppm beryllium, respectively. The incidences of lung reticulum cell sarcomas in the beryllium-exposed rats were not significantly different than in controls. The incidences of reticulum cell sarcoma-bearing rats in the 0, 5, 50, and 500 ppm groups were 12/50, 18/50, 16/50, and 13/50, respectively, for males and 8/50, 11/50, 7/50, and 8/50 for the females; no significant increase in tumor-bearing rats was found. No other treatment-related increases in tumor incidence were observed.

Morgareidge et al. (1976) conducted a long-term feeding study in which groups of 5 male and 5 female beagle dogs (aged 8-12 mo) were fed diets containing 0, 5, 50, or 500 ppm beryllium as beryllium sulfate tetrahydrate for 172 weeks. The basal diet was a commercial dog chow (Purina®) moistened with warm water; the dogs were given access to the food for 1 h per day. Because of overt signs of toxicity, the 500 ppm group was terminated at 33 weeks. At this time, a group of 5 male and 5 female dogs was added to the study and fed a diet containing 1 ppm beryllium; duration of exposure for this group was 143 weeks. Using estimated TWA body weights of 13.0, 12.7, 13.8, and 12.3 kg for males in the 1, 5, 50, and 500 ppm groups, respectively, and 10.2, 10.3, 11.2, and 8.6 kg for females, and the reported average food intake of 300 g/day, the 1, 5, 50, and 500 ppm concentrations correspond to doses of 0.023, 0.12, 1.1, and 12.2 mg/kg-day for male dogs and 0.029, 0.15, 1.3, and 17.4 mg/kg-day for females. The following parameters were used to assess toxicity: daily observations, food consumption, body weight, hematology and serum clinical chemistry (blood samples collected after 1, 3, 6, 16, 18,

24, 30, and 36 mo exposure), urinalysis (samples collected after 1, 3, 6, 18, 24, 30, and 36 mo of exposure), organ weights (heart, liver, kidney, brain, spleen, pituitary, thyroids, adrenals, and gonads), and histopathology of the spleen, thymus, pancreas, lungs, gonads, stomach, small and large intestines, urinary bladder, heart, aorta, muscle, adrenals, thyroids, lymph nodes, salivary glands, gallbladder, liver, kidneys, pituitary, brain, spinal cord, skin, mammary gland, bone marrow, and eyes.

Two moribund animals in the 500 ppm group were sacrificed during week 26; the remainder of the animals in the 500 ppm group were killed during week 33. Overt signs of toxicity observed in the 500 ppm group included lassitude, weight loss, anorexia, and visibly bloody feces, indicating that the MTD is < 500 ppm. Four other animals died during the course of the study or were killed moribund; two dogs died during parturition, and one male and one female dog in the 50 ppm group died. The appearance, behavior, food intake, and body weight gain of the animals in the other beryllium groups did not differ from controls. No beryllium-related hematological, serum chemistry, or urinalysis alterations were observed in the 1, 5, or 50 ppm groups. In the 500 ppm group, a slight anemia (slight decreases in erythrocyte, hemoglobin, and hematocrit; statistical analysis not reported), more apparent in the females than in the males, was observed after 3 and 6 mo exposure; however, there were no alterations in the bone marrow and none of the animals was seriously affected. The authors note that the anemia may have been related to the gastrointestinal tract hemorrhages rather than a direct effect of beryllium on the hematological system. No alterations in organ weights were observed. All animals in the 500 ppm group showed fairly extensive erosive (ulcerative) and inflammatory lesions in the gastrointestinal tract. These occurred predominantly in the small intestine, and to a lesser extent in the stomach and large intestine, and were regarded by the authors as treatment-related. This conclusion is supported by independent review of the study report; the lesions are not considered related to some other cause such as intestinal worms (Goodman, 1997). All of the animals with stomach or large intestinal lesions also had lesions in the small intestine, except for one animal with stomach lesions only. This animal had stomach lesions that were very localized and not very severe. Lesions in the small intestine (4/5 males and 5/5 females) considered treatment-related include desquamation of the epithelium, edema, fibrin thrombi, acute inflammation, subacute/chronic inflammation, necrosis and thinning/atrophy of the epithelium, and ulceration (Goodman, 1997). High-dose animals also showed moderate to marked erythroid hypoplasia of the bone marrow, which the authors also considered treatment-related (Goodman, 1997). Bile stasis and vasculitis in the liver and acute inflammation in the lymph nodes occurring in these animals are attributed to a likely systemic bacterial invasion through the damaged intestinal mucosa. A generalized low-grade septicemia likely initiated kidney damage.

In the 50 ppm group, one female dog died after 70 weeks of treatment. This animal showed gastrointestinal lesions, but less severe, occurring in the same locations and appearing to be the same types as those in dogs administered 500 ppm. The authors stated that the death of this animal appeared related to beryllium administration. Other animals in this treatment group survived until study termination and had no remarkable gross or microscopic findings.

No neoplasms were observed in the beryllium-exposed dogs. Reproductive endpoints are discussed in Section 4.3.

Groups of 52 male and 52 female Long-Evans rats were maintained on a low-metal diet and given drinking water containing 0 or 5 ppm beryllium as beryllium sulfate (presumably tetrahydrate) from weaning to natural death (Schroeder and Mitchener, 1975a). The water also contained 5 ppm chromium III, 50 ppm zinc, 5 ppm copper, 10 ppm manganese, 1 ppm cobalt, and 1 ppm molybdenum. Doses of 0.63 and 0.71 mg/kg-day were calculated for male and female rats, respectively, using estimated TWA body weights of 0.42 and 0.26 kg and EPA (1988) allometric equation for water consumption. The following parameters were used to assess toxicity: body weights (animals weighed at weekly and monthly intervals for the first year, and at 3-mo intervals thereafter); blood glucose; cholesterol and uric acid (blood samples collected from 12 rats/sex after an 18-h fast); urine protein, pH, and glucose; heart weight; gross pathology; and histopathology of heart, lung, kidney, liver, spleen, and tumors. Twenty male and eight female rats in the beryllium group died at 20 mo of age from pneumonia; a similar number of animals in the control group also died from pneumonia.

At 30 days, the male and female rats exposed to beryllium weighed significantly more than the control animals. At 60, 90, 120, and 180 days, the beryllium-exposed male rats weighed significantly less than the controls; no significant alterations in body weight were observed at the other time intervals (150, 360, or 540 days). Because decreases in body weight were generally < 10% and not prolonged, these data indicate the doses may have been close to, but did not reach, the MTD (U.S. EPA, 1986b). No significant alterations in mortality or longevity were observed. Glycosuria (females only) and alterations in serum glucose levels were observed in the beryllium-exposed rats. The alterations in serum glucose levels consisted of significantly lower levels in males aged 475 days and higher levels in males and females aged 719 days. It should be noted that the control rats were at least 50 days older than the beryllium-exposed rats when blood samples were collected, and in the controls, blood glucose levels declined with increasing age. Significantly increased serum cholesterol levels were observed in female rats exposed to beryllium at ages 475 and 719 days. The results of the histological examination were not reported. The alterations in serum glucose, cholesterol levels, and urine glucose levels were not considered adverse because the alterations were not large enough to suggest an impairment in organ function.

The incidence of gross tumors was 4/26 (15%) and 17/24 (70%) in the male and female control rats and 9/33 (27%) and 14/17 (82%) in the male and female rats exposed to beryllium. The incidences of malignant tumors (tumors were considered malignant if there were multiple tumors in the same animal) were 2/26 (7.7%) and 8/24 (33%) in the male and female controls and 4/33 (12%) and 8/57 (14%) in the male and female beryllium-exposed rats. The incidences of gross or malignant tumors in the control and beryllium-exposed groups were not significantly different. It should be noted that in an unpublished report (Schroeder and Nason, 1976), the incidence of gross tumors in male and female beryllium-exposed rats was 4/25 and 13/20 (control data the same as reported in published paper). In the published paper, this is the tumor incidence for tungsten-exposed rats. It is difficult to determine which is the correct tumor incidence data for the beryllium-exposed rats; however, neither set of incidence data is statistically significantly different from controls.

In a lifetime exposure study, groups of 54 male and 54 female Swiss mice were administered 0 or 5 ppm beryllium as beryllium sulfate in drinking water from weaning to natural death (Schroeder and Mitchener, 1975b). The mice were fed low-metal diets and the drinking

water was supplemented with 50 ppm zinc, 10 ppm manganese, 5 ppm copper, 5 ppm chromium III, 1 ppm cobalt, and 1 ppm molybdenum. The 5 ppm water concentration is equivalent to doses of 1.2 mg Be/kg-day for the male and female mice, using an estimated TWA body weight of 0.042 and 0.035 kg and the EPA (1988) allometric equation for water consumption. In the beryllium group, statistically significant alterations in body weight were observed; the alterations included heavier male mice at 30 days and lighter female mice at 90 and 120 days. Overall, the decrease in body weight was < 10%, indicating that the MTD was not reached. No significant alterations in mortality or survival were observed in the beryllium-exposed mice. No alterations in tumor incidence were observed.

Matsumoto et al. (1991) fed groups of 10 male Wistar rats diets containing 0 or 3% beryllium carbonate for 4 weeks. The diet contained adequate amounts of calcium. EPA's (1988) allometric equation for daily food consumption and an estimated TWA body weight of 0.10 kg were used to calculate a dose of 3,700 mg/kg-day beryllium carbonate (480 mg/kg-day beryllium). Body weight and serum calcium, phosphate, protein, alkaline phosphatase, and acid phosphatase levels were the only parameters measured. At 4 weeks, the rats fed the beryllium diet weighed approximately 18% less than the controls (statistical significance not reported). Serum phosphate concentrations and serum alkaline phosphatase activity were significantly lower in the beryllium-exposed rats. No statistically significant alterations in serum calcium or protein levels or serum acid phosphatase activity were observed.

In addition to the recent oral study by Matsumoto et al. (1991) using rats fed diets containing beryllium carbonate, older oral studies by Guyatt et al. (1933) and Kay and Skill (1934) have demonstrated rickets in rats fed diets containing up to 3% beryllium carbonate; however, the bone lesions observed were not attributed to any direct effects from beryllium itself, but to the deprivation of phosphate in the intestine by precipitation as beryllium phosphate.

In a series of experiments conducted by Guyatt et al. (1933), young rats were fed a "normal" stock diet containing 0.125-3.0% beryllium carbonate (13-300 mg/kg-day beryllium using a food factor of 0.05 [U.S. EPA, 1986b] and the authors' estimate that the beryllium carbonate used in the study contained 20% beryllium). It appears that the animals were fed this experimental diet for at least 24-28 days; however, no additional information on the exposure protocol was provided. Decreases in body weight gain, decreases in activity, and a "waddling" gait and arched back were observed in the beryllium-exposed rats, and the severity and onset appeared to be dose-related, but it is not known if these effects were observed in all groups. X-ray examination revealed rickets in rats fed diets of 0.125% beryllium carbonate and higher; a considerable decrease in bone density and an almost complete lack of calcification of epiphyseal cartilage was observed in the $\geq 1\%$ beryllium carbonate diet groups. Histological examination of the femur and tibia showed evidence of decreases in mineral deposition in the metaphysis and reduced amounts of mineral salts in the trabeculae and cortex of the tibia. Decreases in plasma inorganic phosphorus levels, decreases in acid-soluble phosphorus levels in the liver, and decreases in kidney phosphatase levels were observed in the beryllium-exposed rats; no changes in liver inorganic phosphorus levels were observed.

Kay and Skill (1934) fed groups of 8 albino rats (strain and sex not reported) a basal diet ("Bill's stock diet") which contained 0 or 0.5% beryllium carbonate for 21-22 days. Using a food

factor of 0.05 (U.S. EPA, 1986) and the estimate of beryllium content of the beryllium carbonate (20%) from Guyatt et al. (1933), a dose of 50 mg/kg-day beryllium was estimated. Eight groups of rats were fed the beryllium carbonate diets; 5 of the groups also received daily subcutaneous injections of 0.5%-25% sodium glycerophosphate and 2 groups received daily subcutaneous injections of 1% or 10% saline solution. "Excellent skeletal development" was found in the control group. In the beryllium-exposed group (without glycerophosphate or saline injections), severe rickets and decreased blood inorganic phosphorus, "plasma phosphatase," total erythrocyte phosphorus, liver "ester phosphorus," and kidney phosphatase levels were observed. In the beryllium-exposed rats administered glycerophosphate, the severity of the rickets and the decreases in phosphorus levels were diminished; this was not observed in the beryllium-exposed rats administered saline solution.

To assess the effect of beryllium on body weight, Freundt and Ibrahim (1990) administered 0 or 100 ppm beryllium sulfate tetrahydrate in drinking water to groups of 5 female Sprague-Dawley rats for 91 days. Using a TWA body weight of 0.28 kg and a water intake of 0.039 L/day (calculated using EPA's [1988] allometric equation), a dose of 13.9 mg/kg-day beryllium sulfate (0.71 mg/kg-day beryllium) was calculated. The rats were fed a standard diet. The rats were weighed at weekly intervals and food and water consumption was measured weekly. Although the beryllium-exposed rats weighed more than the controls, the difference was not statistically significant. Administration of beryllium in the drinking water also resulted in increases in food intake (approximately 3%-5% higher than controls) and water consumption (approximately 5%-10% higher than controls).

In a dietary exposure study (Goel et al., 1980), a group of eight male albino rats (strain not specified) were fed a standard diet and given 20 mg beryllium nitrate orally every third day for 2.5 months (40 doses administered). A control group of four male rats was fed the standard diet. In the beryllium-exposed rats, a number of histological alterations were observed in the lungs. These included congestion and ruptured ciliated epithelial cells of the respiratory bronchioles, thickened epithelium cells and necrosis in the alveoli, and damage to the arteriole endothelium. The other ingestion studies, as well as the parenteral administration studies, did not report respiratory effects. Although the method was not adequately described, it appears that the beryllium nitrate was placed on the food in a powder form; thus, it is possible that the animals inhaled some of the beryllium.

4.2.2. Inhalation Exposure

Although a number of chronic studies in laboratory animals have been conducted with beryllium compounds, few have been done using modern criteria for high-quality toxicology studies. In addition, whereas several laboratory animal species (such as mice, dogs, and monkeys) respond to beryllium exposure with several features of human CBD, no laboratory animal model fully mimics all features of human CBD. In particular, the animal models fail to demonstrate a progressive granulomatous pulmonary response with a concomitant beryllium-specific immune response. In addition, no chronic studies are available on nonneoplastic effects of beryllium oxide, the most environmentally relevant form.

Reeves et al. (1967) exposed 150 male and 150 female Sprague-Dawley rats for 7 h/day, 5 days/week to $34.25 \mu\text{g Be/m}^3$ as beryllium sulfate aerosol (average particle size was $0.118 \mu\text{m}$, electron microscopy) for up to 72 weeks, with 3 of each sex sacrificed monthly during exposure. An equal number of control rats were exposed to distilled water aerosol. Lung weights were markedly increased in the exposed rats, and an inflammatory lung response (characterized as a marked accumulation of histiocytic elements and thickened and distorted alveolar septa) was noted, as accumulation of alveolar macrophages. A proliferative response was also noted, progressing from hyperplasia to alveolar adenocarcinomas in 100% of the exposed rats at 13 mo, compared to 0% of the controls. Histopathologic examination was limited to the lungs. The authors noted that 8 male and 4 female rats in the control group and 9 male and 17 female rats in the beryllium group died during the course of the study. The plateau body weight in the beryllium-exposed female rats was approximately 25% less than found in the controls (statistical significance not reported).

Lung granulomas, inflammation, and adenomas were also observed in a group of 127 Sherman rats (males and females combined) exposed to $28 \mu\text{g/m}^3$ beryllium as beryllium sulfate aerosol for 8 h/day, 5.5 days/week for up to 6 mo and killed in groups of 5-15 immediately after the end of exposure, or approximately monthly for up to 18 mo postexposure (Schepers et al., 1959). There was a lag period for the development of granulomas, with most of these lesions developing several months after the end of exposure.

Vorwald and Reeves (1959) exposed Sherman rats (number and sex not reported) via the inhalation route to aerosols of beryllium sulfate at 6 and $54.7 \mu\text{g Be/m}^3$ for 6 h/day, 5 days/week for an unspecified duration. Animals were sacrificed periodically and examined histopathologically. Initially, inflammation consisted of histiocytes, lymphocytes, and plasma cells scattered throughout the lung parenchyma. Following more prolonged exposures, more focal lesions consisting primarily of histiocytes were observed. Multinucleated giant cells were also observed. Thickened alveolar walls and fibrotic changes were also observed. Lung tumors, primarily adenomas and squamous cell cancers, were observed in the animals sacrificed after 9 mo of this exposure regime.

Similar results to those of Vorwald and Reeves were observed in a study by Reeves and Deitch (1969, as reviewed by EPA, 1987b). In this study, groups of 20-25 Charles River CD rats were exposed to $35.66 \mu\text{g Be/m}^3$ as beryllium sulfate for 35 h/week; the mean particle size was $0.21 \mu\text{m}$ (d_{ae}). The exposure durations were 800 h (5 groups), 1,600 h (2 groups), and 2,400 h (1 group). Age at the initiation of exposure appeared to be a more important variable for tumor development than was exposure duration. The lung tumor incidence (19/22, 86%) for young rats exposed for 3 mo was the same as in rats exposed for 18 mo (13/15, 86%) but was higher than in older rats exposed for 3 mo (3-10/20-25, 15%-40%). Tumors were typically observed after a latency period of 9 mo. In the beryllium-exposed rats, the epithelial hyperplasia observed at 1 mo progressed to metaplasia at 5-6 mo and anaplasia by 7-8 mo.

Stokinger et al. (1953) conducted a chronic study in which groups of 14 dogs, 5 cats, 10 male rabbits, and 120 male rats were exposed to $186 \mu\text{g Be/m}^3$ as beryllium fluoride for 6 h/day, 5 days/week for 207 calendar days, with some intermediate sacrifices. There was no control group for any species. Three of the dogs and 73 rats died during the experiment, with all deaths by day

70 for the dogs and day 19 for the rats. Dogs exhibited significant increases in plasma fibrinogen after 9-17 days of exposure, followed by a second peak at 117 or more days of exposure. Decreases in red blood cell counts and hemoglobin concentration and increases in mean corpuscular volume were observed in rabbits and dogs. Histopathological lesions were observed only in the lungs, and occurred in most animals of all of the tested species. Lesions included an infiltration of large monocytes, polymorphonuclear leukocytes in the alveoli, and interstitial infiltration of monocytes and lymphocytes.

Stokinger et al. (1950) exposed rats, dogs, cats, rabbits, guinea pigs, hamsters, monkeys, and goats via inhalation to 40, 430, or 2,000 $\mu\text{g Be/m}^3$ as beryllium sulfate for 6 h/day, 5 days/week for 100, 95, or 51 days, respectively. No animals died following exposure to the low concentration. Following exposure to 430 $\mu\text{g Be/m}^3$, 23/47 rats, 1/5 cats, 2/24 rabbits, and 2/34 guinea pigs died but all dogs, monkeys, and goats survived. Mortality was higher in animals exposed to 2,000 $\mu\text{g Be/m}^3$. Signs of toxicity included weight loss and anemia. All histopathological lesions were confined to the lungs, with an interstitial and intraalveolar infiltration of monocytes, polymorphonuclear leukocytes, lymphocytes, and plasma cells. Macrophages containing cellular debris were observed within the alveoli. The exposure levels at which histopathological lesions were observed were not specified for each species, therefore no NOAEL or LOAEL could be assigned.

In a study to test the carcinogenicity of beryllium ores, Wagner et al. (1969) exposed groups of 12 male squirrel monkeys (*Saimiri sciurea*), 60 male CR-CD rats, 30 male Greenacres Controlled Flora (GA) rats, and 48 male Golden Syrian hamsters to 0 or 15 mg/m^3 bertrandite or beryl for 6 h/day, 5 days/week for 17 mo (rats and hamsters) or 23 mo (monkeys). The test atmospheres generated from the bertrandite ore ($\text{Be}_4\text{Si}_2\text{O}_7[\text{OH}]_2$; 1.4% beryllium) and beryl ore ($\text{B}_3\text{Al}_2\text{Si}_6\text{O}_{18}$; 4.14% beryllium) contained 210 and 620 $\mu\text{g Be/m}^3$, respectively, and the geometric mean diameters of the particles were 0.27 μm (geometric standard deviation of 2.4) and 0.64 μm (geometric standard deviation of 2.5). Both ores contained very high silicon dioxide levels (63.9% by weight). Exposed and control monkeys, rats, and hamsters were serially sacrificed upon completion of 6 and 12 mo of exposure; rats and hamsters at the 17th month, and monkeys at the 23rd month. Five control rats and five rats from the 12th- and 17th-month exposure groups were sacrificed in order to determine the free-silica content of the lung tissue. At exposure termination, beryllium concentrations in the lungs were 18.0 and 83 $\mu\text{g/g}$ fresh tissue in the bertrandite- and beryl-exposed rats, 14.1 and 77.4 $\mu\text{g/g}$ fresh tissue in the bertrandite- and beryl-exposed hamsters, and 33 and 280 $\mu\text{g/g}$ fresh tissue in the bertrandite- and beryl-exposed monkeys. Free silica (SiO_2) levels in the rat lungs were 30-100 times higher in the beryllium ore-exposed rats than in the controls. Increased mortality was observed in the monkeys (11%), rats (13%), and hamsters (25%) exposed to either bertrandite or beryl ore, with the highest mortality rates in the bertrandite ore-exposed animals (no further details provided). No significant alterations in body weight gain were observed in the monkeys or hamsters.

In the rats, decreased body weight gains (terminal body weights were 15% lower compared to controls) were observed beginning after 6 mo of exposure, and from 12 mo to exposure termination at 17 mo. In the beryl-exposed rats, small foci of squamous metaplasia or tiny epidermoid tumors were observed in the lungs of 5/11 rats killed after 12 mo of exposure. At exposure termination, lung tumors were observed in 18/19 rats (18 had bronchiolar alveolar cell

tumors, 7 had adenomas, 9 had adenocarcinomas, and 4 had epidermoid tumors). Additional alterations in the lungs included loose collections of foamy macrophages and cell breakdown products, lymphocyte infiltrates around the bronchi, and polymorphonuclear leukocytes and lymphocytes present in most of the bronchiolar-alveolar cell tumors. In the bertrandite-exposed rats, granulomatous lesions composed of several large, tightly packed, dust-laden macrophages were observed in all rats exposed for 6, 12, or 17 mo. No tumors were observed. Neoplastic or granulomatous pulmonary lesions were not observed in the control rats. In the beryl- and bertrandite-exposed monkeys, the histological alterations consisted of aggregates of dust-laden macrophages, lymphocytes, and plasma cells near respiratory bronchioles and small blood vessels. No tumors were found. In the bertrandite-exposed hamsters, granulomatous lesions consisting of tightly packed, dust-laden macrophages were observed after 6 mo, and the number did not increase after 17 mo. These alterations were not observed in the beryl-exposed or control hamsters. Atypical proliferation and lesions, which were considered bronchiolar alveolar cell tumors except for their size, were observed in the hamsters after 12 mo of exposure to beryl or bertrandite. After 17 mo of exposure, these lesions became larger and more adenomatous in the beryl-exposed hamsters. It should be noted that silicosis was not observed in any of the animals exposed to the beryllium ores that contained a large amount of free silica. No significant gross or histologic alterations were observed in the thymus, spleen, liver, or kidneys of the beryllium-exposed rats, hamsters, and monkeys.

In a monkey carcinogenicity study (Vorwald, 1968), a group of 7 male and 9 female rhesus monkeys (*Macaca mulatta*) (aged 18 mo) were exposed to $35 \mu\text{g Be}/\text{m}^3$ beryllium sulfate mist 6 h/day, 5 days/week. The author notes that the "exposure was interrupted, often for considerable periods of time, in order to maintain the best possible overall well-being of the animal, to prevent a threatening acute beryllium pneumonitis, and to favor survival to old age or at least long enough for the inhaled beryllium to exert its maximal chronic effects in terms of epithelial proliferation, metaplasia, and cancer." The exposure schedule was presented in a figure, but it was difficult to determine the exposure protocol from this figure. The longest exposure was for 4,070 h. Most of the exposure was during the first 4.5 years of the study, with an approximate 6-mo exposure 2.5 years later. Four animals died within the first 2 mo of the study; the cause of death was acute chemical pneumonitis. Lung cancer was observed in 8 of the 12 remaining animals. The first tumor was observed in a monkey 8 years of age exposed for 3,241 hours. The tumors were described as a gross mass located in either the hilar area or more peripheral portions of the lung, or as small and large tumors scattered irregularly throughout the pulmonary tissue.

A single-exposure inhalation study of beryllium metal in F344/N rats resulted in a 64% incidence of lung carcinomas over the lifetime of the animals (Nickell-Brady et al., 1994). Groups of 30 males and 30 females were administered a single, nose-only exposure to a beryllium metal aerosol (MMAD = $1.4 \mu\text{m}$, GSD = 1.9) at $500 \text{ mg}/\text{m}^3$ for 8 min, $410 \text{ mg}/\text{m}^3$ for 30 min, $830 \text{ mg}/\text{m}^3$ for 48 min, or $980 \text{ mg}/\text{m}^3$ for 39 min. Control rats were exposed to filtered air alone. Mean lung burdens resulting from these exposures were 40, 110, 360, and $430 \mu\text{g}$ of beryllium, respectively. Tumors became apparent by 14 mo after exposure, and the incidence (apparently for all groups combined) was 64% over the lifetime of the rats. Multiple tumors were frequently found; the majority were adenocarcinomas, and some were $> 1 \text{ cm}$. The tumors were analyzed for gene mutations (see Section 4.4.3).

Intratracheal instillation studies are discussed in Section 4.4.2.

4.3. REPRODUCTIVE/DEVELOPMENTAL STUDIES—ORAL AND INHALATION

4.3.1. Oral Exposure

There are limited data on the reproductive and developmental toxicity of beryllium compounds following oral exposure. In the chronic dog oral exposure study conducted by Morgareidge et al. (1976) (described in Section 4.2), the male and female dogs exposed to 1, 5, or 50 ppm beryllium sulfate in the diet (0.023, 0.12, and 1.1 mg/kg-day for males and 0.029, 0.15, and 1.3 mg/kg-day for the females) were housed together at the time of the second heat after treatment initiation, allowed to mate and wean (at 6 weeks of age) their pups, which were then returned to community floor pens (with the exception of the first litter, which was killed 5 days after whelping). The number of pregnant females for 0, 1, 5, and 50 ppm were as follows: 3, 2, 5, and 3. Treated females had between 1 and 3 litters; controls had 1-4, each litter by the same sire. First-litter pups surviving to postnatal day 5 were sacrificed for soft tissue gross examination and were stained for evaluation of skeletal malformations. Pups from subsequent litters were grossly examined at weaning. Beryllium did not appear to adversely affect reproductive or developmental endpoints (number of pregnancies, number of pups, number of live pups, pup weight) in the beryllium-exposed dogs. No beryllium-related decreases in post-natal survival (day 7 or weaning) were observed. The authors reported no gross or skeletal abnormalities in the surviving first litter pups, but data were not shown; stillborn or cannibalized pups dying within the first few postnatal days were not examined.

4.3.2. Inhalation Exposure

Only limited information is available on potential reproductive and developmental effects of beryllium, but there appear to be no effects following exposure via environmentally relevant routes. Savitz et al. (1989) found no association between occupational exposure to beryllium and the risk of stillbirth, preterm delivery, or small-for-gestational-age infants in a case-control study using National Natality and National Fetal Mortality Survey data. Analyses were conducted for 2,096 mothers and 3,170 fathers of stillbirths, 363 mothers and 552 fathers of preterm babies, and 218 mothers and 371 fathers of small-for-gestational-age babies. For beryllium, analyses were conducted only for paternal exposure, not for maternal exposure. In light of the small population exposed to beryllium, case-control studies have limited sensitivity for reproductive effects.

No animal experiments of the developmental toxicity of inhaled beryllium are available. No standard 2-generation reproductive studies have been carried out.

4.3.3. Parenteral Administration

Several studies (as reviewed by U.S. EPA, 1991b) have tested the reproductive and developmental toxicity of beryllium following intratracheal instillation and intraperitoneal

injection. Clary et al. (1975) conducted a continuous breeding experiment in which male and female Sprague-Dawley rats received a single intratracheal administration of 200 µg beryllium as beryllium oxide (calcined at 960°C in the first experiment and at 500°C in the second experiment). Groups of four or five females and two males were placed together for mating. In the first experiment, groups of eight exposed rats and four controls were sacrificed after the first, second, and fourth pregnancies, and at 12 and 15 mo. No alterations in average number of pregnancies, number of live or dead pups per litter, lactation index, or fetal body weights were observed. In the second experiment, 10 exposed and 10 control rats were sacrificed at 12 mo after exposure. There was no adverse effect of beryllium in either experiment. Indeed, significant increases in the number of live pups/female were observed in the dosed groups.

Developmental effects (increased fetal mortality, decreased fetal body weight, internal abnormalities, and delayed neurodevelopment) were observed in the offspring of rodents following intratracheal or intraperitoneal administration of beryllium chloride, beryllium oxide, or beryllium sulfate during gestation. Mathur et al. (1987) administered intravenous injections of 0.021 mg/kg Be as beryllium nitrate to mated Sprague Dawley rats (n = 5-8/group) (1/10th the LD₅₀) on postcoital day 1, 11, 12, 13, 15, or 17. Rats were laparotomized on gestation days 10 and 20 and then allowed to deliver. All pups died within 2-3 days of birth and all pups in the group injected on postcoital day 11 died in utero, but these effects may have been due to the repeated surgeries.

4.4. OTHER STUDIES

4.4.1. Mechanistic Studies

Considerable research has investigated the mechanism of CBD and attempted to identify an appropriate animal model for CBD. An appropriate animal model for CBD is one that forms immune granulomas following the inhalation of beryllium, demonstrates beryllium specificity of the response, and mimics the progressive nature of the human disease. These immune granulomas are distinct from granulomas formed by foreign-body reactions (Haley, 1991). Immune granulomas result from persistent antigenic stimulation, while foreign-body granulomas result from persistent irritation. Histologically, foreign-body granulomas consist predominantly of macrophages and monocytes, and small numbers of lymphocytes. By contrast, immune granulomas are characterized by larger numbers of lymphocytes, primarily T lymphocytes (known as T cells). T cells in granulomas are primarily antigen-specific T-helper cells, which are recognized by the presence of the CD4 antigen on their cell surfaces. The predominance of T cells in immune granulomas and the responsiveness to beryllium in skin patch tests (reviewed in Kreiss et al., 1994) indicate that the immune response in CBD is primarily cell-mediated.

Numerous studies with laboratory animals have demonstrated that exposure to beryllium often results in chronic granulomatous inflammation of the lung that is often progressive, even after cessation of beryllium exposure (Sendelbach et al., 1986; Haley et al., 1989, 1990). However, not all of these lesions can be attributed to an immune inflammation.

4.4.1.1. *Animal Models for CBD*

Granulomas in beryllium-exposed rats are formed by foreign-body reactions, rather than immune mechanisms, and so are not a good model for CBD. Male F344/N rats exposed to a beryllium metal aerosol at $800,000 \mu\text{g}/\text{m}^3$ for 50 min developed an acute necrotizing, hemorrhagic, exudative pneumonitis and intraalveolar fibrosis, with the most severe response reported at day 14 postexposure (Haley et al., 1990). After a period of decreased response, the inflammation progressed to chronic active inflammation. The chronic lung lesions were characterized by severe alveolar macrophage, alveolar epithelial hyperplasia, and interstitial fibrosis. These granulomatous lesions had only low numbers of lymphocytes, and lymphocyte levels in the BAL were also not elevated. Chronic inflammation and Type II cell hyperplasia were observed at initial lung burdens (ILB) as low as $1.8 \mu\text{g}$ ($4,700 \mu\text{g}/\text{m}^3$ beryllium for 30 min) with no effect at an ILB of $0.32 \mu\text{g}$ ($8,600 \mu\text{g}/\text{m}^3$ for 14 min) and with an exposure-related severity (Finch et al., 1994). Preliminary experiments also found no evidence of beryllium-induced proliferation of splenic lymphocytes obtained from rats exposed to an initial lung burden of $50 \mu\text{g}$ beryllium as beryllium metal, and tested in the BeLT at 210 days postexposure (Haley, 1991). Similarly, the lungs of F344 rats exposed for 1 h to $0.013 \mu\text{g Be}/\text{m}^3$ as beryllium sulfate aerosol had injury-related cell proliferation, Type II alveolar cell hyperplasia, and infiltrates of interstitial macrophages, but few lymphocytes (Sendelbach et al., 1986). The response was largely resolved by 3 weeks postexposure.

Hart et al. (1984) found no effect on lymphocyte level in BAL of F344 rats exposed for 1 h to $447 \mu\text{g Be}/\text{m}^3$ as beryllium oxide aerosol heat-treated at 560°C , and the resulting inflammatory lesions of the lung consisted of macrophages and polymorphonuclear (PMN) leukocytes, with few lymphocytes. Effects in rats exposed to beryllium oxide calcined at about $1,000^\circ\text{C}$ ($1\text{--}100 \mu\text{g Be}/\text{m}^3$ for 30–180 min) were milder, with small granulomatous lesions consisting primarily of foamy macrophages (Sanders et al., 1975). The absence of lymphocytes in beryllium-induced lesions in these studies shows that acute beryllium disease occurs in the rat, but the rat is not an appropriate model for CBD, because it does not mount an immune response to inhaled beryllium. F344 rats previously immunized by injection of beryllium sulfate and then exposed 2 weeks later to a single dose of beryllium sulfate via intratracheal instillation developed pulmonary granulomas 6 weeks after exposure, but the granulomas were resolving by 12 weeks postexposure (Votto et al., 1987). Total lung tissue exhibited an increase in both T- and B-lymphocytes, and T-helper cells were increased in BAL fluid. This system may provide a rat model for CBD, but the study did not show a beryllium-specific immune response.

Mice may be an appropriate model for CBD, although not all aspects of the disease have been replicated in this species. BAL fluid of mice (sex not reported) preimmunized with beryllium sulfate and then administered a single intratracheal dose of beryllium sulfate had increased lymphocytes at 1 to 8 weeks postexposure, primarily because of increased T-helper cells, although Bursa (B) cells were also increased (Huang et al., 1992). Interstitial inflammation and granuloma formation were observed, but these changes only occurred at 8 mo postexposure, not earlier, and had resolved by 10 mo. This protocol did not produce lesions in BALB/c or C57B1 mice, suggesting that genetic differences at the H2 major histocompatibility locus (MHC) could be responsible for differences in sensitivity. Nikula et al. (1997) exposed female A/J mice and C3H/HeJ mice to a beryllium metal aerosol (nose-only exposure) for 90 min, resulting in mean

initial lung burdens of 49 and 62.50 μg , respectively. At 28 weeks after exposure, the mice had a marked, multifocal granulomatous pneumonia with mild interstitial fibrosis. The histopathological lesions were similar for both mouse strains. The interstitial aggregates exhibited lymphocyte proliferation and contained elevated numbers of T-helper cells; the observed histopathological lesions may have been due to toxic and foreign-body properties of beryllium and an immune response. However, beryllium-specific proliferation of lymphocytes was not observed in the BeLT using lymphocytes from peripheral blood, the spleen, or bronchial lymph nodes. Although these two studies differed in the beryllium compound studied and neither demonstrated a beryllium-specific response, the observed granulomas did have an immune component.

The guinea pig appears to model certain aspects of CBD. An immune granulomatous lung disease was observed in strain 2 guinea pigs that received a single intratracheal injection of 1.8 mg beryllium as beryllium oxide (Barna et al., 1984a). The calcining temperature was not reported, but an earlier study by the same authors used beryllium oxide calcined at 560°C (Barna et al., 1981). The granulomas contained interstitial infiltrates of lymphocytes and other cells, but fibrosis was not observed. Lesions developed by 6 weeks, with all animals affected by 10 weeks and a marked decrease in the incidence and severity of the lesions by 1.5 years postexposure. Spleen and lymph node cells proliferated in response to beryllium sulfate stimulation in the BeLT, although tests with other metals were not conducted to show beryllium sensitivity. Results from the BeLT with BAL lymphocytes were not informative, because the unstimulated cells incorporated large amounts of tritiated thymidine and were refractory to further stimulation by mitogens (Barna et al., 1984b). However, an increased percentage of T lymphocytes was observed in BAL fluid from treated guinea pigs. By contrast, strain 13 guinea pigs, which differ from strain 2 only at the MHC Ia locus, had no significant increase in granulomatous lung disease compared to controls, and no evidence of beryllium sensitization. These studies show that intratracheal instillation of beryllium oxide can induce in guinea pigs both immune granulomas containing a T lymphocyte component, and a beryllium-specific immune response. However, the effect has not yet been demonstrated under physiological conditions (inhalation exposure), and specificity for beryllium over other metals has not been demonstrated.

The beagle dog appears to model most aspects of human CBD (Haley et al., 1989). Granulomatous lesions and lung lymphocyte responses consistent with those observed in humans with CBD were observed following a single exposure to beryllium oxide aerosol generated from beryllium oxide calcined at 500°C or 1,000°C. The aerosol was administered to the dogs perinasally at 10 mg Be/m³ for 5-40 min to attain initial lung burdens of 6 or 18 μg beryllium/kg body weight. Perivascular and peribronchiolar infiltrates of lymphocytes and macrophages were observed histopathologically 8 and 32 days postexposure, with a peak response observed at 64 days. These lesions progressed to microgranulomas with areas of granulomatous pneumonia and interstitial fibrosis. Although there was considerable interindividual variation, lesions were generally more severe in the dogs exposed to material calcined at 500°C. The lesions declined in severity after 64 days postexposure. The percentage and numbers of lymphocytes in BAL fluid was increased at 3 mo postexposure in dogs exposed to either dose of beryllium oxide calcined at 500°C, but not in dogs exposed to the material calcined at the higher level. Beryllium specificity of the immune response was demonstrated by positive results in the BeLT, although there was considerable interindividual variation. Positive results were observed with BAL lymphocytes only

in the group with a high ILB of the material calcined at 500°C, but positive results with peripheral blood lymphocytes were observed at both doses with material calcined at both temperatures.

In a follow-up experiment, control dogs and those exposed to beryllium oxide calcined at 500°C were allowed to rest for 2.5 years, and then re-exposed to filtered air (controls) or beryllium oxide calcined at 500°C for ILB target of 50 µg BeO/kg body weight (Haley et al., 1992). Immune responses of blood and BAL lymphocytes, and lung lesions in dogs sacrificed 210 days postexposure, were compared with results following the initial exposure. The severity of lung lesions was comparable under both conditions, suggesting that a 2.5-year interval was sufficient to prevent cumulative pathologic effects. Conradi et al. (1971) found no exposure-related histological alterations in the lungs of six beagle dogs exposed to a range of 3,300-4,380 µg Be/m³ as beryllium oxide calcined at 1,400°C for 30 min, once per month for 3 mo. Because the dogs were sacrificed 2 years postexposure, the long time period between exposure and response may have allowed for the reversal of any beryllium-induced changes. Alternatively, the high calcining temperature may have contributed to the low toxicity, continuing the trend observed with beryllium oxide calcined at 500°C and 1,400°C.

Haley et al. (1994) exposed male cynomolgus monkeys (*Macaca fascicularis*) to either beryllium metal or beryllium oxide calcined at 500°C by intrabronchiolar instillation as a saline suspension. Lymphocyte counts in BAL fluid were significantly increased in monkeys exposed to beryllium metal on postexposure days 14 to 90, but only on postexposure day 60 in monkeys exposed to beryllium oxide. The lungs of monkeys exposed to beryllium metal had lesions characterized by interstitial fibrosis, Type II cell hyperplasia, and lymphocyte infiltration; some monkeys exhibited immune granulomas. Similar lesions were observed in monkeys exposed to beryllium oxide, but the incidence and severity were much less. BAL lymphocytes from monkeys exposed to Be metal, but not from monkeys exposed to beryllium oxide, proliferated in response to beryllium sulfate in the BeLT. In an experiment similar to the one conducted with dogs, Conradi et al. (1971) found no effect in monkeys (*Macaca irus*) exposed via whole-body inhalation for three 30-min monthly exposures to a range of 3,300-4,380 µg Be/m³ as beryllium oxide calcined at 1,400°C. The lack of effect may have been related to the long period (2 years) between exposure and sacrifice, or to low toxicity of beryllium oxide calcined at such a high temperature. The data from Haley et al. (1994) show that beryllium can induce immune granulomas and beryllium sensitization in monkeys via intrabronchiolar instillation, although this was not shown using a physiologically relevant route.

4.4.1.2. Genetics of Beryllium Sensitivity

Evidence from a variety of sources shows that genetic susceptibility plays a role in the development of CBD. Early occupational studies proposed that CBD was an immune reaction with a genetic component, based on the high sensitivity of certain individuals and the lack of CBD in others who were exposed to levels several orders of magnitude higher (Sterner and Eisenbud, 1951). Animal studies support these results. Immune granulomas were observed in strain 2 guinea pigs, but not in strain 13 guinea pigs, which differ from strain 2 only at the MHC Ia locus (Barna et al., 1984a). Similarly, beryllium inhalation caused immune granulomas in A/J mice, but not in BALB/c or C57B1 mice, which have different MHC class II genes (Huang et al., 1992).

These studies suggest that differences in CBD susceptibility are related to differences at the MHC locus.

MHC class II antigens and functional IL2 receptors are needed in order for BAL CD4+ T cells from patients with CBD to proliferate in vitro in response to beryllium stimulation (Saltini et al., 1989). This requirement, known as class II restriction, is typical of the response of CD4+ T cells to soluble antigens, but not nonspecific mitogens. In other words, the T cells only respond to the antigen (in this case, beryllium or beryllium plus some protein) in association with MHC class II molecules on the surface of the antigen-presenting cell. Granuloma formation has been hypothesized to result from a cytokine amplification loop involving macrophages, lymphocytes, and other factors (Newman, 1996).

Recent studies have identified a genetic marker linked to CBD susceptibility. The MHC class II region includes the HLA-DR, DQ, and DP genes. Richeldi et al. (1993) reported a strong association between the MHC class II allele HLA-DP β 1, which has a glutamate at position 69, and the development of CBD in beryllium-exposed workers. This marker was found in 32/33 of the workers who developed CBD, but in only 14/44 similarly exposed workers without CBD. Stubbs et al. (1996) also found a biased distribution of HLA-DP β 1 alleles in beryllium-sensitized subjects, with the glutamine-69 allele present in 86% of the sensitized subjects but in only 48% of exposed, nonsensitized subjects. They also found a biased distribution of the MHC class II HLA-DR gene but found no association with specific amino acid changes. Thus, neither of these markers are completely specific for CBD; the data do support a strong genetic contribution to CBD susceptibility, and these markers may be useful for screening for sensitive workers. It is also not clear if the association between either allele and CBD is a causal one. Preliminary findings show that the anti-HLA-DR antibody blocked beryllium-specific lymphocyte proliferation, while an anti-HLA-DP antibody had a minimal effect. It is not yet clear which, if either, of these class II genes interact directly with the beryllium ion, although the antibody inhibition data suggest that the HLA-DR gene product may be involved in the presentation of beryllium to T lymphocytes. However, Richeldi et al. (1993) noted that structure-function studies of MHC class II molecules indicate that the amino acid change associated with CBD may affect an amino acid that plays a critical role in antigen binding. The more common allele of HLA-DP β 1 has a positively charged amino acid (lysine) at position 69, while the glutamine-69 variant is negatively charged at this site and could directly interact with the beryllium ion. Nonetheless, the high percentage (~30%) of exposed workers without CBD who had this allele suggests that other factors also contribute to the development of CBD. The beryllium exposure level plays at least some role, since the overall prevalence of CBD in exposed workers is 2%-5%, while the prevalence at certain highly exposed tasks is as much as 15% (Kreiss et al., 1993a, 1996).

4.4.1.3. Relationship Between Beryllium Speciation and Toxicity

The toxicity of beryllium compounds is related to the solubility and surface area of the compound. For example, in a subacute inhalation study with female monkeys (*Macacus mullata*), beryllium fluoride was markedly more toxic than beryllium sulfate, which was somewhat more toxic than beryllium phosphate (Schepers, 1964). Beryllium metal appeared to induce a greater toxic response than beryllium oxide following intrabronchiolar instillation in cynomolgus

monkeys, as evidenced by more severe lung lesions, a larger effect on BAL lymphocyte counts, and a positive response in the BeLT with BAL lymphocytes only after treatment with beryllium metal (Haley et al., 1994). Comparable doses were calculated based on comparable levels of the Be^{2+} ion, based on an assumed dissolution rate for Be metal, rather than on comparable levels of instilled beryllium. This form of normalization was chosen in light of data suggesting that the toxicity of beryllium metal results from a thin surface layer of beryllium oxide on the metal particles (Hoover et al., 1989). Occupational studies also show compound-specific differences in beryllium toxicity, but are less clear about whether beryllium metal or beryllium oxide is more toxic, probably because of variability in particle size. Eisenbud and Lisson (1983) found a higher prevalence of CBD in people who worked with beryllium metal than in those who worked with beryllium oxide, and Sterner and Eisenbud (1951) found a much higher prevalence of CBD in people who worked with beryllium oxide than in those who worked with other beryllium compounds. By contrast, Cullen et al. (1987) found a greater frequency of CBD in workers exposed to beryllium oxide fumes than those exposed to beryllium metal, but the small particle size of the fume compared to the beryllium metal dust may have contributed to the higher toxicity of the beryllium oxide in this study.

The temperature at which beryllium oxide is calcined influences its solubility, and hence its toxicity. Haley et al. (1989a) found more severe lung lesions and a stronger immune response in beagle dogs receiving a single inhalation exposure to beryllium oxide calcined at 500°C than in dogs receiving an equivalent initial lung burden of beryllium oxide calcined at 1,000°C. The higher toxicity of beryllium oxide calcined at 500°C has been attributed to its greater surface area compared to the material calcined at 1,000°C (Finch et al., 1988). These authors found that the *in vitro* cytotoxicity to Chinese hamster ovary (CHO) cells and cultured lung epithelial cells of 500°C beryllium oxide was greater than that of 1,000°C beryllium oxide, which was greater than that of beryllium metal. However, when toxicity was expressed in terms of particle surface area, the cytotoxicity of all three forms was similar. Similar results were observed in a study comparing the cytotoxicity of beryllium metal particles of various sizes to cultured rat alveolar macrophages, although specific surface area did not entirely predict cytotoxicity (Finch et al., 1991). The similar solubilities of beryllium metal particles and beryllium oxide are attributed to a fine layer of beryllium oxide that coats the metal particles (Hoover et al., 1989).

In an *in vitro* study with dog alveolar macrophage cultures, Eidson et al. (1991) found that uptake of beryllium oxide by macrophages was independent of the calcination temperature, but soluble beryllium sulfate was poorly taken up. Intracellular dissolution of the oxide correlated with cytotoxicity, and was higher for the material calcined at 500°C. The authors concluded that beryllium oxide is phagocytized by the macrophages, dissolved in lysosomes, and becomes cytotoxic once sufficiently high dissolved concentrations are achieved. Extracellular soluble beryllium was concluded to be noncytotoxic.

4.4.2. Carcinogenicity Studies—Parenteral and Dermal Administration

A number of studies have examined the carcinogenic potential of beryllium and beryllium compounds in animals following intratracheal, intravenous, intramedullary, and intracutaneous administration. The results of these studies have been extensively reviewed by EPA (1987b,

1991b). Lung tumors have been observed in rats following a single intratracheal instillation of beryllium metal, passivated beryllium metal (99% beryllium, < 1% chromium), beryllium-aluminum alloy (62% beryllium), or beryllium hydroxide. Beryllium alloys containing $\leq 4\%$ beryllium did not result in increases in lung tumors. Lung tumor incidences of 11%-51% were observed in rats following intratracheal instillation of beryllium oxide fired at high, low, and medium temperatures. The types of lung tumors found in animals receiving intratracheal instillations of beryllium included adenocarcinomas, adenomas, squamous cell carcinoma, and malignant lymphoma. Osteosarcomas have been observed in rabbits and possibly in mice following intravenous or intramedullary injection of zinc beryllium silicate, beryllium oxide, beryllium phosphate, or beryllium metal. Tumors have not been observed following intracutaneous injection of beryllium sulfate; after accidental introduction of beryllium oxide, beryllium phosphate, or beryllium-containing fluorescent phosphors into the skin; or following percutaneous administration of beryllium compounds. Granulomatous ulcerations were observed when the beryllium penetrated the epidermal layer of the skin.

4.4.3. Genotoxicity

The genotoxicity of beryllium has been previously reviewed by EPA (1987b) and recently reviewed by IARC (1993). Most studies have found that beryllium chloride, beryllium nitrate, beryllium sulfate, and beryllium oxide did not induce gene mutations in bacterial assays, with or without metabolic activation. In the case of beryllium sulfate, all mutagenicity studies (Ames [Simmon, 1979; Dunkel et al., 1984; Arlauskas et al., 1985; Ashby et al., 1990]; *E. coli* pol A [Rosenkranz and Poirer, 1979]; *E. coli* WP2 uvr A [Dunkel et al., 1984]) and *Saccharomyces cerevisiae* (Simmon, 1979) were negative, with the exception of results reported for *Bacillus subtilis* rec assay (Kada et al., 1980; Kanematsu et al., 1980) and *E. coli* rec assay (Dylevoi, 1990). Beryllium sulfate did not induce unscheduled DNA synthesis in primary rat hepatocytes and was not mutagenic when injected intraperitoneally in adult mice in a host-mediated assay using *Salmonella typhimurium* (Williams et al., 1982).

Beryllium nitrate was negative in the Ames assay (Tso and Fung, 1981; Kuroda et al., 1991) but positive in a *Bacillus subtilis* rec assay (Kuroda et al., 1991). Beryllium chloride was negative in a variety of studies (Ames [Ogawa et al., 1987; Kuroda et al., 1991]; *E. coli* WP2 uvr A [Rossman and Molina, 1986]; and *Bacillus subtilis* rec assay [Nishioka, 1975]). In addition, beryllium chloride failed to induce SOS repair in *E. coli* (Rossman et al., 1984). However, positive results were reported for *Bacillus subtilis* rec assay using spores (Kuroda et al., 1991), *E. coli* KMBL 3835; lacI gene (Zakour and Glickman, 1984) and hprt locus in Chinese hamster lung V79 cells. Beryllium oxide was negative in the Ames assay and *Bacillus subtilis* rec assays (Kuroda et al., 1991).

Gene mutations have been observed in mammalian cells cultured with beryllium chloride (Miyaki et al., 1979; Hsie et al., 1979a,b) and culturing mammalian cells with beryllium chloride (Vegni-Talluri and Guiggiani, 1967), beryllium sulfate (Brooks et al., 1989; Larramendy et al., 1981) or beryllium nitrate has resulted in clastogenic alterations. Additionally, beryllium sulfate has the ability to induce morphological transformations in cultured mammalian cells. Data on the in vivo genotoxicity of beryllium are limited to two studies. Beryllium sulfate (1.4 and 2.3 g/kg,

50% and 80% of median lethal dose) administered by gavage did not induce micronuclei in the bone marrow of CBA mice, although a marked depression of erythropoiesis suggestive of bone marrow toxicity was evident 24 h after dosing. No mutations were in *p53* or *c-raf-1* and only weak mutations were detected in *K-ras* in lung carcinomas from F344/N rats given a single nose-only exposure to beryllium metal (Nickell-Brady et al., 1994). The authors concluded that the mechanisms for the development of lung carcinomas from inhaled beryllium in the rat do not involve gene dysfunctions commonly associated with human non-small-cell lung cancer.

4.5. SYNTHESIS AND EVALUATION OF MAJOR NONCANCER EFFECTS AND MODE OF ACTION—ORAL AND INHALATION

4.5.1. Oral Exposure

There are no reliable data on the oral toxicity of beryllium in humans. The database for animal oral exposure studies is composed of short-term and chronic studies, many of which tested low doses of beryllium and did not find any adverse effects.

Gastrointestinal lesions and bone marrow hypoplasia were observed in male and female dogs fed diets containing 1-17 mg/kg-day and 12-17 mg/kg-day beryllium sulfate, respectively, for approximately 3 years (Morgareidge et al., 1976). Chronic oral exposure of rats (0.4-43 mg/kg-day) and mice (1.2 mg/kg-day) to beryllium sulfate did not result in any adverse effects (Morgareidge et al., 1975, 1977; Schroeder and Mitchener, 1975a,b).

“Beryllium rickets” have been observed in rats exposed to beryllium carbonate (13-300 mg/kg-day) in the diet for 3-4 weeks (Guyatt et al., 1933; Kay and Skill, 1934). It has been suggested that the rickets are the result of decreased absorption of phosphorus through the gastrointestinal tract, rather than a direct effect on bones or alterations in calcium balance. This is supported by the findings of Matsumoto et al. (1991) on rats fed beryllium carbonate (480 mg/kg-day) in the diet. One hypothesis is that, in the gut, the beryllium binds to soluble phosphorus and forms an insoluble beryllium phosphate that cannot be absorbed.

The oral studies in animals suggest that the gastrointestinal and the skeletal systems are target organs for beryllium. In dogs exposed to beryllium sulfate, the gastrointestinal tract is a sensitive target and lesions appear to be induced in the gut at doses less than those for bone marrow hypoplasia. Gastrointestinal effects were not observed in rats or mice exposed to dietary beryllium sulfate, and the gastrointestinal tract was not examined in the beryllium carbonate studies. It is not known if exposure to beryllium compounds other than beryllium carbonate will result in rickets, because the available studies on beryllium sulfate (the only other beryllium compound with available oral toxicity data) did not examine the skeletal system or measure serum phosphate levels. Schroeder and Mitchener (1975a) noted that rickets were not observed in their beryllium-exposed rats, but the criteria used to assess potential rachitic effects were not reported. Morgareidge et al. (1976) did not mention the occurrence of rickets in dogs that were observed daily and who underwent histological examination of the bone.

The potential of beryllium to induce developmental and/or reproductive effects has not been adequately assessed. In the only oral exposure study examining reproductive or developmental endpoints, beryllium did not affect fertility or pup survival, weight, or skeletal formation (Morgareidge et al., 1976). However, only small numbers of animals were evaluated, and visceral examinations of pups, examination of dying pups, or postnatal development were not evaluated. Developmental endpoints may be important to evaluate because, as with other metals, beryllium may cross the placenta and there is the potential for greater gastrointestinal absorption in young animals. There are no multigeneration studies, nor are there studies of male reproductive toxicity.

Beryllium sensitization progressing to CBD is the critical effect in humans exposed by inhalation. Oral exposure studies in animals have not evaluated measures of immune response or dysfunction.

The dog appears to be the species most relevant for extrapolation of dose-effect to humans. Dogs appear to model most aspects of CBD in humans. The dog is typically a better model than the rodent for the absorption kinetics of elements in humans. In addition, the dog appears to be more sensitive to beryllium than are rats, showing greater effects at comparable doses.

4.5.2. Inhalation Exposure

In humans, the lung is the primary target of inhalation exposure to beryllium. Exposure to levels at or near mean values of $1 \mu\text{g}/\text{m}^3$ for an indeterminate period of time may result in the development of a chronic inflammatory lung disease (CBD) characterized by the formation of granulomas (Cotes et al., 1983; Cullen et al., 1987; Kreiss et al., 1996). These granulomas result from an immune reaction, primarily based on cell-mediated immunity. A genetic component to CBD susceptibility has been identified (Richeldi et al., 1993). The toxicity of beryllium compounds increases with increasing solubility (Finch et al., 1988; Haley et al., 1989a). Beryllium oxide calcined at 500°C is more soluble, more toxic, and has a greater surface area than beryllium calcined at $1,000^\circ\text{C}$. The toxicity of inhaled aerosolized beryllium metal appears to resemble that of beryllium oxide calcined at 500°C because of a thin layer of oxide on the beryllium metal particles (Hoover et al., 1989).

An animal model of human CBD is defined by the development of immune granulomas, a beryllium-specific immune response, and a disease progression that mimics the human disease. Based on these criteria in single-exposure studies, the beagle dog appears to model several aspects of CBD (Haley et al., 1989a). Monkeys (Haley et al., 1994), mice (Huang et al., 1992), and guinea pigs (Barna et al., 1984a), although they have not been studied in as great detail, also appear to develop immune granulomas. Rats form granulomas after inhaling beryllium compounds, but the granulomas do not have an immune component and rats do not mount a beryllium-specific immune response (Finch et al., 1994; Haley et al., 1990; Hart et al., 1984). Using mice and guinea pigs gives the advantage of being able to use larger numbers of animals in experiments, but of these two species, a beryllium-specific immune response has been shown only in guinea pigs. No exposure-response studies have been published using species that are

appropriate models for CBD, and all studies using appropriate models have been conducted only with acute exposures.

4.6. WEIGHT-OF-EVIDENCE EVALUATION AND CANCER CHARACTERIZATION—SYNTHESIS OF HUMAN, ANIMAL, AND OTHER SUPPORTING EVIDENCE, CONCLUSIONS ABOUT HUMAN CARCINOGENICITY, AND LIKELY MODE OF ACTION

The evidence considered in assessing the potential carcinogenicity of beryllium to humans includes cohort mortality studies of workers at beryllium processing facilities, studies of entrants on the BCR, and inhalation, oral, and parenteral studies in animals.

Increases in lung cancer mortality have been observed in cohort mortality studies of beryllium processing workers (Ward et al., 1992; Wagoner et al., 1980; Mancuso, 1979, 1980) and entrants on the BCR (Steenland and Ward, 1991; Infante et al., 1980). No increases in other types of cancer were found, but increases in deaths from nonmalignant respiratory disease were also observed. When the beryllium-exposed cohort was subdivided into groups based on length of time since first exposure, it was found that the increase in lung cancer mortality was due to deaths in workers with a latency of ≥ 25 years (Ward et al., 1992; Wagoner et al., 1980). Lung cancer mortalities were also clustered among workers exposed for < 1 year or for 1-4 years. This statistic is misleading because approximately 50% of the workers in the cohort were employed for < 1 year and 75% were employed for < 5 years (Ward et al., 1992).

The results of many of these studies have been criticized (BISAC, 1997; MacMahon, 1994; U.S. EPA, 1987b; Saracci, 1985). EPA (1987b, 1991b) considered the studies conducted prior to 1987 to be insufficient to assess the carcinogenic potential of beryllium in humans. Although the design of the Ward et al. (1992) study corrected a number of the shortcomings of the older studies, the interpretation of the study results is limited by the assumption used to account for lung cancer deaths due to cigarette smoking, the lack of job history data that would support quantitative exposure assessment, the lack of control for potential exposure to other carcinogens, including coexposure to sulfuric or hydrofluoric acid mists during employment in the beryllium industry or nonconcurrent exposure to other carcinogens during employment outside of the beryllium industry, and the relatively small increases in lung cancer risks.

The issue of potential confounding by exposure to acid mists and vapors has been raised by BISAC (1997), which attributed the elevated SMRs at the Lorain facility (Ward et al., 1992) to confounding by exposure to high concentrations of sulfuric acid mist. Exposure to sulfuric acid mist, however, has not been strongly associated with lung cancer. In its review of the information regarding occupational exposures to mists and vapors from sulfuric acid and other strong inorganic acids (hydrochloric, nitric, and phosphoric acids), IARC (1992) concluded that occupational exposure to strong inorganic acid mists containing sulfuric acid is carcinogenic to humans (Group 1). According to IARC, several occupational studies associated exposure to mists containing sulfuric acid with laryngeal cancer; a few studies reported an association with lung cancer and even fewer with nasal sinus cancer. No quantitation of exposure was available for most of the studies. The quantitation in the one study that provided this type of information

included only a portion of the exposure period and did not account for initially higher exposures. No studies of the carcinogenicity of sulfuric acid mists in animals are available.

An additional recent review of the carcinogenicity of mists containing sulfuric acid has been conducted by a group of epidemiologists, including occupational epidemiologists (Sathiakumar et al., 1997). Most of the reviewed studies were also cited in the IARC (1992) review and none were published subsequent to the IARC review. The conclusions reached by these epidemiologists—that mists of sulfuric acid should not be classified as a “definite human carcinogen”—differ from those reached by IARC. Sathiakumar et al. (1997) pointed out that the assessment of sulfuric acid exposures in the occupational studies was inadequate, and control of confounding due to multiple occupational exposures and by smoking and alcohol was lacking or possibly inadequate. Sathiakumar et al. (1997) concluded that the studies provide no persuasive evidence for a causal relationship between sulfuric acid mists and lung cancer. The majority of lung cancer SMRs in the studies reporting a positive association were in the range 1.18 to 1.39. The authors stated that such weak associations could be explained by confounding by smoking and/or occupational exposures to other substances, including asbestos, PAH, radon, arsenic, nickel, and chromium. In addition, there was no clear evidence of increasing risk with increasing duration of exposure or higher exposure category. Data for nasal and other respiratory cancers was so limited as to preclude a meaningful evaluation of the strength of association or of dose-response. For laryngeal cancer, the occupational studies (both cohort and case-control) suggested a moderate association with exposure to sulfuric acid mists. Rate ratios in the positive studies ranged from 1.3 to 30. Although there were limitations in the data, the associations between occupational exposure to mists of sulfuric acid and cancer of the larynx could not be wholly explained by chance or confounding by alcohol and smoking. The data suggested a possible dose-response relationship. Sathiakumar et al. (1997) concluded that although the data suggest causality, it is possible that some correlate of exposures to sulfuric acid mists causes larynx cancer, and that therefore the current epidemiological data do not warrant classifying sulfuric acid mists as a definite human carcinogen.

Thus, the evidence for an association between sulfuric acid mist and lung cancer is weak and has limitations similar to those for beryllium: poor or no quantitation of exposure and possible confounding by other occupational exposures and smoking. SMRs for lung cancer in cohorts exposed occupationally to sulfuric acid mist are similar to those in cohorts exposed occupationally to beryllium. A stronger association is seen between occupational exposure to sulfuric acid and laryngeal cancer. No association with laryngeal cancer has been seen for occupational exposure to beryllium, but for beryllium, virtually all the studies are mortality studies, which are not optimal for larynx cancer because of the relatively low fatality rate for this type of cancer.

The studies of lung cancer in workers exposed occupationally to beryllium and/or sulfuric acid or other acid mists do not, for the most part, categorize the type of cancer. The data are therefore insufficient to determine whether different types of lung cancer may be associated with beryllium exposure versus sulfuric acid exposure.

Exposures to hydrofluoric acid or hydrogen fluoride also are potential confounders at some of the beryllium processing facilities, including the Reading plant (Ward et al., 1992;

BISAC, 1997). Information regarding the potential carcinogenicity of these compounds was not available. IARC (1992) considered hydrofluoric acid to be a weak inorganic acid and did not assess it in the monograph on strong inorganic acids.

Regardless of the shortcomings of the epidemiological studies of beryllium exposure, the results of all the follow-up mortality studies on the same cohort and of the BCR cohort studies are suggestive of a causal relationship between beryllium exposure and an increased risk of lung cancer. The increased incidences of lung cancers among workers with acute beryllium disease (presumably these workers were exposed to very high concentrations of beryllium), the higher incidences of lung cancers among workers first employed when exposure levels were very high, a consistent finding of lung cancer excesses in six of seven beryllium processing facilities, and the occurrence of the highest risks for lung cancer in plants where the risk for nonmalignant respiratory disease is the highest strengthen this conclusion.

IARC (1993; Vainio and Rice, 1997) considered the epidemiological data as sufficient evidence in humans for the carcinogenicity of beryllium and compounds. IARC (1993) concluded that the issue of adjustments for smoking had been handled adequately, and stated that a limitation of the most recent cohort studies was the absence of discussion of potential exposure to other lung carcinogens, although "there is no evidence that other lung carcinogens were present." EPA, however, considers that the issues of incomplete smoking data and exposure to other potential lung carcinogens are not completely resolvable with the data currently available, and therefore concludes that the evidence of carcinogenicity of beryllium and compounds is limited in humans.

Inhalation exposure to beryllium has resulted in significant increases in lung cancer in rats and monkeys (Nickell-Brady et al., 1994; Reeves et al., 1967; Reeves and Deitch, 1969; Vorwald, 1968; Wagner et al., 1969). These observations support a possible causal association noted in the occupational studies.

Oral exposure studies in rats (Morgareidge et al. 1975, 1977; Schroeder and Mitchener, 1975a) and an oral study in mice (Schroeder and Mitchener, 1975a,b) did not find significant increases in tumor incidences. It should be noted that all three studies tested relatively low doses and no toxic effects were observed at any dose tested. Thus, the MTD was not achieved.

Based on the limited evidence of carcinogenicity in humans exposed to airborne beryllium (lung cancer) and sufficient evidence of carcinogenicity in animals (lung cancer in rats and monkeys inhaling beryllium, lung tumors in rats exposed to beryllium via intratracheal instillation, and osteosarcomas in rabbits and possibly mice receiving intravenous or intramedullary injection), beryllium would be reclassified from a B2 (inadequate human data, present IRIS database) to a B1 probable human carcinogen (limited human data) using criteria of the 1986 Guidelines for Carcinogen Risk Assessment. Using the 1996 proposed Guidelines for Carcinogen Risk Assessment, inhaled beryllium would be characterized as a "likely" carcinogen in humans, and the human carcinogenic potential of ingested beryllium "cannot be determined."

4.7. SUSCEPTIBLE POPULATIONS

4.7.1. Possible Childhood Susceptibility

A number of factors may differentially affect the response of children to toxicants such as beryllium and compounds. These factors include diet and physical environment as well as maturation of physiological and biochemical processes. In general, children have higher gastrointestinal absorption and are more susceptible to the effects of metals (for example, lead; Mushak, 1991) than are adults. Also, metals may cross the placenta, affecting the developing fetus. It seems reasonable that these generalizations would apply to beryllium, but there are no substantiating data available.

4.7.2. Possible Gender Differences

The extent to which men differ from women in susceptibility to beryllium metal and beryllium compounds is not known. Although some gender differences have been observed in oral animal studies with respect to reticulum cell sarcomas (Morgareidge et al., 1975), body weight alterations in rats and mice, glycosuria, and incidence of gross tumors in controls and exposed rats (Schroeder and Mitchener, 1975a,b), the quality of the studies precludes their significance. Male and female dogs developed the same types of gastrointestinal lesions at the same site following chronic beryllium ingestion (500 ppm as beryllium sulfate tetrahydrate). One of five female dogs showed similar lesions, while no males responded, at the lower dose of 50 ppm (Morgareidge et al., 1976).

Compared to oral exposure conditions, fewer gender differences were observed via inhalation. Reeves et al. (1967) observed differences in plateau body weight between females and males in beryllium-exposed female rats compared to controls.

Data are insufficient to draw definitive conclusions regarding gender differences in response to beryllium exposure.

5. DOSE-RESPONSE ASSESSMENTS

5.1. ORAL REFERENCE DOSE (RfD)

5.1.1. Choice of Principal Study and Critical Effect—With Rationale and Justification

There are no human oral exposure studies that could be used to derive an RfD for beryllium.

There are a number of long-term animal studies (Guyatt et al., 1933; Kay and Skill, 1934; Schroeder and Mitchener, 1975a,b; Morgareidge et al., 1975, 1976, 1977) reported for several species (rats, mice, dogs) ingesting beryllium sulfate and/or beryllium carbonate. Morgareidge et

al. (1976) is chosen as the principal study and lesions of the small intestine of dogs is the critical effect.

No adverse effects were observed in rats (Morgareidge et al., 1975, 1977) exposed to ≤ 500 ppm beryllium sulfate in the diet (≤ 37 -43 mg/kg-day) or in rats and mice (Schroeder and Mitchener, 1975a,b) exposed to 5 ppm beryllium sulfate in drinking water (0.63 and 0.71 mg/kg-day for rats and 1.2 mg/kg-day for mice). These studies are limited by free-standing NOAELs (i.e., highest dose tested is NOAEL), flaws in study design or executions, or inadequate documentation of the study results.

"Beryllium rickets" have been observed in rats exposed to beryllium carbonate (13-300 mg/kg-day) in the diet for 3-4 weeks (Guyatt et al., 1933; Kay and Skill, 1934). It has been suggested that the rickets are the result of decreased absorption of phosphorus through the gastrointestinal tract, rather than a direct effect on bones or alterations in calcium balance. This is supported by the findings of Matsumoto et al. (1991) with rats fed beryllium carbonate (480 mg/kg-day) in the diet. One hypothesis is that, in the gut, the beryllium binds to soluble phosphorus and forms an insoluble beryllium phosphate that cannot be absorbed.

Morgareidge et al. (1976) found that dogs fed 500 ppm beryllium as beryllium sulfate tetrahydrate (12 and 17 mg/kg-day for males and females, respectively) developed gastrointestinal lesions, most severely in the small intestine; weight loss, anorexia and lassitude were also observed in these animals. Exposure to 500 ppm was terminated after 33 weeks and the animals were killed in a moribund condition. A 10-fold lower beryllium concentration (50 ppm; 1.1 and 1.3 mg/kg-day in males and females, respectively) resulted in similar, but less severe, gastrointestinal tract lesions as those seen in one female in the 500 ppm group dying during week 70. The remaining animals at this dose level survived until study termination at approximately 3 years and showed no histopathological alterations in the gastrointestinal tract related to treatment. A NOAEL of approximately 0.1 mg/kg-day and frank-effect level (FEL) of 12 mg/kg-day for gastrointestinal tract lesions, anorexia, and weight loss in moribund dogs are determined. It is, however, difficult to discern whether the 1.3 mg/kg-day level should also be considered a FEL, because one animal died, or whether it is more appropriately considered a LOAEL, since while one animal was affected after a year of treatment, the other animals at the same level survived 2 years longer without adverse gastrointestinal pathology. Alternatively, some may think this one animal overly sensitive and discount it. However, the gastrointestinal lesions in this animal were of the same type and occurred in the same region, but with lesser severity, as in the higher dose group.

Therefore, the critical effect is small intestinal lesions in dogs in Morgareidge et al. (1976). A dose of 0.1 mg/kg-day is a NOAEL, 12 mg/kg-day is a FEL, and it is difficult to ascertain the LOAEL dose.

5.1.2. Methods of Analysis—Benchmark Dose

For small intestinal lesions, dose-response information is available for more than one dose level and can be used to determine the BMD₁₀, thereby decreasing the reliance on the one animal at 50 ppm.

For BMD calculations, the dose was converted from ppm beryllium to mg/kg-day using food intake reported by the authors as 300 g/day and the time-weighted average body weight (kg) for each sex/dose group for the study (females: 0, 0.029, 0.15, 1.3, 17.4; males: 0, 0.023, 0.12, 1.1, 12.2 mg/kg-day). The average of the doses (0, 0.026, 0.135, 1.2, 14.8 mg/kg-day) and the combined male and female incidence for small intestinal lesions (0/10, 0/10, 0/10, 1/10, 9/10) were modeled by the exponential polynomial, THRESH, and Weibull models. A 10% change (extra risk) was chosen as the benchmark response. The exponential polynomial model gave a fit to the data (*p* value for goodness-of-fit = 0.94). The BMD (the lower 95% confidence bound on the concentration from the MLE [maximum likelihood estimate], 10% extra risk) obtained for these data with this model was 0.46 mg/kg-day (MLE = 1.4 mg/kg-day). For the THRESH model, the BMD₁₀ was 0.47 mg/kg-day (MLE = 1.2); the *p* value for goodness of fit is 1.0. The Weibull model was also applied with similar results (*p* value for goodness-of-fit = 0.96; MLE = 1.3; BMD₁₀ = 0.46 mg/kg-day). The BMD₁₀ of 0.46 mg/kg-day is used for all subsequent quantitation in the RfD dose-response assessment.

5.1.3. RfD Derivation—Including Application of Uncertainty Factors (UF) and Modifying Factors (MF)

A 300-fold uncertainty factor (UF) is applied to the BMD₁₀ for lesions in the small intestines of male and female dogs for derivation of the RfD. This UF is composed of 10-fold each for intra- and interspecies extrapolation and a threefold factor for database deficiencies. Although there are several chronic oral animal studies, there is a lack of human toxicity data by the oral route, and reproductive/developmental and immunotoxicologic endpoints have not been adequately assessed in animals. Database gaps include lack of adequate studies for evaluation of reproductive and developmental toxicity (including multigenerational studies, studies on male reproductive toxicity, teratology, and postnatal development) owing to the possible crossing of the placenta and greater absorption of beryllium in young animals. In addition, oral studies examining immunologic endpoints, the most sensitive endpoint by the inhalation route, are lacking. Since the principal study is of chronic duration and a benchmark dose is used, there are no uncertainty factors for duration or NOAEL/LOAEL extrapolation. No modifying factor is proposed for this assessment. It should be noted that the RfD is imprecise to perhaps an order of magnitude.

$$\text{RfD} = 0.46 \text{ mg/kg-day} / 300 = 2\text{E-}3 \text{ mg/kg-day}$$

5.2. INHALATION REFERENCE CONCENTRATION (RfC)

5.2.1. Choice of Principal Study and Critical Effect—With Rationale and Justification

There is an extensive body of evidence documenting beryllium sensitization and CBD as the most sensitive effect of inhalation exposure to beryllium, and explaining the unusual exposure-response pattern. The Kreiss et al. (1996) occupational exposure study, which identified a LOAEL(HEC) of $0.20 \mu\text{g}/\text{m}^3$, and the Eisenbud et al. (1949) community monitoring study, which identified a NOAEL(HEC) of $0.01\text{--}0.1 \mu\text{g}/\text{m}^3$, were selected as the co-principal studies. Although the method of identifying CBD cases in the Eisenbud et al. (1949) study was relatively insensitive compared to modern methods, this study has the advantage of being conducted with the general population, rather than a worker population. In addition, because the incidence of CBD was evaluated at different distances from the plant (and hence at different estimated exposure levels), this was the only study that was able to identify a NOAEL for CBD. The NOAEL(HEC) range reflects the uncertainty associated with the estimations of exposure level.

Occupational exposure studies by Cullen et al. (1987) and Cotes et al. (1983) identified low LOAEL(HEC)s for CBD. Using the beryllium case registry definition of CBD, Cullen et al. (1987) identified a LOAEL(HEC) of $0.19 \mu\text{g}/\text{m}^3$. Although the LOAEL(HEC) identified in this study was similar to that found in Kreiss et al. (1996), the Cullen et al. (1987) study was not selected as a principal study because no historical exposure monitoring data were available and worker exposure levels were estimated using a small amount of monitoring data. Cotes et al. (1983) reported a LOAEL(HEC) of $0.033 \mu\text{g}/\text{m}^3$, but the CBD used in this study was not well defined. This study was not selected as a principal study because only two cases of CBD were identified and the exposure concentrations were estimated using area samplers rather than personal and/or breathing zone samplers.

5.2.2. Methods of Analysis—NOAEL/LOAEL

A NOAEL(HEC) of $0.01\text{--}0.1 \mu\text{g}/\text{m}^3$ was observed based on general population inhalation exposure to beryllium near the Lorain beryllium plant (0.75 miles), using insensitive screening methods (Eisenbud et al., 1949). An occupational study by Kreiss et al. (1996) found a LOAEL of $0.55 \mu\text{g}/\text{m}^3$ (LOAEL[HEC] of $0.20 \mu\text{g}/\text{m}^3$) using more sensitive screening methods.

A benchmark concentration (BMC) analysis could not be conducted for two reasons. First, neither study provided exposure-response information for more than one exposure level. Second, CBD is a sensitization disease, and the maximum susceptible population appears to be about 16% of the exposed population (Kreiss et al., 1993b). Therefore, a response level of 10% would correspond to 1.6% (i.e., $\text{BMC}_{1.6}$) of the susceptible population developing the disease. No studies have yet been conducted evaluating the exposure-response in the subset of the population that appears to be genetically susceptible to CBD.

Calculation of the HEC for the occupational studies is as follows. The occupational LOAEL value was adjusted for the default occupational ventilation rate and for the intermittent work week schedule using the equation:

$$\text{LOAEL(HEC)} = \text{LOAEL } (\mu\text{g}/\text{m}^3) \times (10 \text{ m}^3 \text{ per 8-h workshift}) / (20 \text{ m}^3 \text{ per day}) \times 5 \text{ days} / 7 \text{ days}$$

Thus, a LOAEL of $0.55 \mu\text{g}/\text{m}^3$ (Kreiss et al., 1996) corresponds to a LOAEL(HEC) of $0.20 \mu\text{g}/\text{m}^3$.

5.2.3. RfC Derivation—Including Application of Uncertainty Factors (UF) and Modifying Factors (MF)

The available data suggest that only a small percentage of the population (1%-5%) appears to be susceptible to CBD (Kreiss et al., 1994). Because individuals developing beryllium sensitization and CBD are the most sensitive subpopulation, an uncertainty factor of 1 was used to account for human variability. An uncertainty factor of 1 was also used to adjust for the less-than-chronic exposure duration of the Kreiss et al. (1996) study; use of this uncertainty factor is supported by the evidence that the occurrence of CBD does not appear to be related to exposure duration. Because the screening method used in the Kreiss et al. (1996) study was more sensitive than the methods used in the Eisenbud et al. (1949) study, the RfC was derived from the LOAEL (Kreiss et al., 1996) with an uncertainty factor of 3 to account for the sensitive nature of the subclinical endpoint (beryllium sensitization). A database uncertainty factor of 3 was used to account for the poor quality of exposure monitoring in the co-principal studies and other epidemiology studies that assessed the incidence of beryllium sensitization and CBD among exposed workers and community residents. Although there are no developmental studies or two-generation reproduction studies, a limited continuous breeding study found that beryllium does not cause reproductive or developmental effects following intratracheal administration (Clary et al., 1975). In addition, systemic distribution of beryllium is less than 1% (U.S. EPA, 1987b), and any systemic effects would be expected to occur at exposure levels much above the very low levels at which CBD is observed.

No modifying factor is proposed for this assessment (MF = 1).

$$\text{RfC} = 0.2 \mu\text{g}/\text{m}^3 \div 10 = 0.02 \mu\text{g}/\text{m}^3, \text{ or } 2\text{E-}2 \mu\text{g}/\text{m}^3$$

5.3. CANCER ASSESSMENT

The cancer dose-response assessment based on the occupational study of Wagoner et al. (1980) that is presented in this section was derived by EPA (1987b), verified in 1988, and has been on IRIS since that time. Newer studies, particularly the occupational study of Ward et al. (1992), have been considered as the basis for a dose-response assessment, but share a limitation with the Wagoner et al. (1980) study—lack of individual exposure monitoring or job history data that would support a more definitive exposure assessment. NIOSH has recently completed a lung cancer case-control study nested within a cohort mortality study of beryllium manufacturing workers at the Reading beryllium processing facility. The study developed an exposure matrix and calculated airborne beryllium exposure concentrations, and thus may provide the best available basis for a quantitative cancer estimate. The study is currently in peer review. Rather than calculate an interim quantitative estimate based on the Ward et al. (1992) data and poorly

defined exposure estimates, it is recommended that the existing unit risk based on the Wagoner et al. (1980) study be retained until the NIOSH assessment can be evaluated as the basis for a quantitative estimate.

5.3.1. Choice of Study/Data—With Rationale and Justification

5.3.1.1. Oral Exposure

The oral carcinogenicity database is considered inadequate for assessing the carcinogenic potential of ingested beryllium. Derivation of a quantitative cancer risk estimate is therefore precluded. In general, the oral animal studies (Schroeder and Mitchener, 1975a,b; Morgareidge et al., 1975, 1976, 1977) did not find statistically significant increases in tumors upon ingestion of beryllium sulfate.

5.3.1.2. Inhalation exposure

There is limited information reported on beryllium exposure levels for the seven beryllium processing facilities that were examined in the cohort mortality studies. Prior to 1950, when exposure levels of $\leq 2 \mu\text{g}/\text{m}^3$ were mandated by the Atomic Energy Commission, beryllium levels at the Lorain and Reading facilities (facilities with the highest lung cancer mortality rates) were very high. NIOSH (1972) estimated that the lower-bound estimate of the median exposure concentration exceeded $100 \mu\text{g}/\text{m}^3$ and concentrations in excess of $1,000 \mu\text{g}/\text{m}^3$ were commonly found (Eisenbud and Lisson, 1983). In 1947 and 1948, beryllium concentrations of 590-43,300 $\mu\text{g}/\text{m}^3$ were measured at the Lorain facility. Beryllium levels exceeding the Atomic Energy Commission's permissible levels were frequently found after 1950. At the Elmore, OH, facility, time-weighted average (TWA) beryllium levels of 3.8-9.5, 6.8-19.1, and 23.1-54.6 $\mu\text{g}/\text{m}^3$ were found in 1953, 1956, and 1960, respectively (Zielinski, 1961). Another study of this facility found that in 1960 and 1966, beryllium concentrations ranged from < 0.1 to $1,050 \mu\text{g}/\text{m}^3$ depending on the production area; the average and median levels for all areas were 60.3 and 28.4 $\mu\text{g}/\text{m}^3$, respectively, in 1960 and 18.1 and 11.4 $\mu\text{g}/\text{m}^3$ in 1966 (Cholak et al., 1967). The available exposure data suggest that beryllium processing workers could have been exposed to a wide range of beryllium concentrations depending on the facility where they worked, decade they were employed, and the type of work performed. The lack of monitoring data relating cancer risk to beryllium exposure levels or reliable exposure surrogates is reason for concern; however, it does not preclude the use of the human exposure data estimated by NIOSH (range of median exposure levels inside plants [100 - $1,000 \mu\text{g}/\text{m}^3$]) for quantitative cancer risk estimates.

With the possible exception of the Wagner et al. (1969) study, the results of the animal carcinogenicity studies are incompletely reported and are not of sufficient quality to be used as the basis of quantitative cancer risk estimates. Because Wagner et al. (1969) exposed the rats to ores with relatively low beryllium levels and high levels of silicon dioxide, this study would not be an appropriate basis for a risk estimate for general population exposure to beryllium.

5.3.2. Dose-Response Data

Dose-response data are inappropriate for oral exposure. Dose-response data for inhalation include the occupational exposure study of a cohort of workers exposed to beryllium at the Reading facility (Wagoner et al., 1980). Lung cancer SMRs were elevated, particularly for workers hired prior to 1950 when exposures to beryllium were very high, and who were followed for at least 25 years (SMR = 187). EPA (1987b) further analyzed the data and concluded that the adjusted SMRs, while still elevated, were not statistically significant. The adjustments accounted for differences in smoking habits between the cohort and the U.S. population and for the use of older vital statistics, and eliminated an ineligible cancer death. The adjusted lung cancer deaths for the subcohort followed for at least 25 years ranged from 13.91 to 14.67, in comparison with 20 observed, resulting in SMRs or relative risks of 1.44 to 1.36, respectively.

| Beryllium concentration in workplace ($\mu\text{g}/\text{m}^3$) | Ratio of years of exposure to years at risk (f/L) | Effective dose ($\mu\text{g}/\text{m}^3$) | 95% upper-bound estimate of relative risk | Unit risk per $\mu\text{g}/\text{m}^3$ |
|---|---|---|---|--|
| 100 | 1.00 | 21.92 | 1.98 | 1.61E-3 |
| | | | 2.90 | 1.79E-3 |
| | 0.25 | 5.48 | 1.98 | 6.44E-3 |
| | | | 2.09 | 7.16E-3 |
| 1,000 | 1.00 | 219.18 | 1.98 | 1.61E-4 |
| | | | 2.09 | 1.79E-4 |
| | 0.25 | 54.79 | 1.98 | 6.44E-4 |
| | | | 2.09 | 7.16E-4 |

5.3.3. Dose Conversion

Not applicable by the oral route.

With respect to the inhalation route, the effective dose was determined by adjusting for duration of daily (8/24 h) and annual (240/365) exposure, and the ratio of exposure duration to duration at risk, i.e., f years out of a period of L years at risk (from onset of employment to termination of follow-up). Two values of f/L were used in the calculations, namely, f/L = 1 and = 0.25. An f/L of 1 would avoid overestimating the risk (but could underestimate the risk) if the observation by Reeves and Deitch (1969)—that tumor yield depends not on the length of exposure but on age at exposure—is valid. For a given “effective” dose d and a relative risk R, the carcinogenic potency (q_1^*) is calculated by the formula $B = (R - 1) \times 0.036/d$, where 0.036 is the estimated lung cancer mortality rate in the U.S. population. The risk estimates were based on

the data of Wagoner et al. (1980) in which the smoking-adjusted, expected lung cancer deaths were found to range from 13.91 to 14.67, in comparison to 20 observed. Relative risk estimates of 1.36 ($p > 0.05$) and 1.44 ($p > 0.05$) were derived and the 95% upper confidence limits of these estimates, 1.98 and 2.09, respectively, were used to estimate the lifetime cancer risk ($q1^*$).

5.3.4. Extrapolation Method(s)

Not applicable for the oral route.

With respect to inhalation studies in humans, the response is measured in terms of the relative risk of the exposed cohort of individuals as compared with the control group. The mathematical model employed for low-dose extrapolation assumes that for low exposures the lifetime probability of death from cancer, P_o , may be represented by the linear equation

$$P_o = A + B_H x$$

where A is the lifetime probability in the absence of the agent and x is the average lifetime exposure to environmental levels in units such as $\mu\text{g}/\text{m}^3$. The factor B_H is the increased probability of cancer associated with each unit increase of x , the agent in air.

5.3.5. Oral Slope Factor and Inhalation Unit Risk

An oral slope factor was not derived.

With regard to the inhalation route of exposure, data from the epidemiological study by Wagoner et al. (1980) and the industrial hygiene reviews by NIOSH (1972) and Eisenbud and Lisson (1983) have been used to develop a cancer risk estimate associated with exposure to air contaminated with beryllium. Two upper-bound relative risk estimates, 1.98 and 2.09, calculated from the human data ($p < 0.05$ for both relative risk values), have been used in the calculations. In recognition of the greater uncertainty associated with the exposure estimation, four different "effective" levels of exposure that reflect various uncertainties, along with two relative risk estimates, have been used in the present calculations. As a result, eight potency estimates have been calculated ranging from $1.6\text{E-}4$ per $\mu\text{g}/\text{m}^3$ to $7.2\text{E-}3$ per $\mu\text{g}/\text{m}^3$, with the geometric mean of the eight estimates being $2.4\text{E-}3$ per $\mu\text{g}/\text{m}^3$. This "unit risk" estimate could be considered an upper-bound estimate of the cancer risk because low-dose linearity is assumed in the extrapolation and the 95% upper-confidence limits (1.98 and 2.09) are used in the calculations.

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE RESPONSE

6.1. HAZARD IDENTIFICATION

Beryllium is a light, stable, bivalent metal belonging to the alkaline earth family. It is used in metal alloys, in particular beryllium-copper alloy, and in high-performance products in the metallurgical, aerospace, and nuclear industries. The primary anthropogenic emission source of beryllium is the combustion of coal and fuel oil, which releases beryllium-containing particulates and fly ash. The general population is exposed to beryllium through inhalation of air and consumption of food and drinking water.

There are no human data on the oral toxicity of beryllium. Chronic oral studies in rodents generally have not shown adverse effects of ingested beryllium (Morgareidge et al., 1975, 1977; Schroeder and Mitchener, 1975a,b). However, these studies have had several limitations in design and execution. A long-term (≈ 3 -year) oral study in dogs indicates the gastrointestinal tract, particularly the small intestine, is the target organ for ingested beryllium (Morgareidge et al., 1976).

The lung is the primary target of inhalation exposure to beryllium. Beryllium sensitization and CBD have been observed following occupational exposure and in residents living near a beryllium manufacturing facility (Kreiss et al., 1996; Eisenbud et al., 1949). CBD is a well-characterized granulomatous immune disease that occurs in a susceptible subset of the population. A genetic component of CBD has been identified. This genetic marker identifies most, but not all, of the CBD cases, and a portion of those with the marker do not develop CBD after exposure to beryllium, indicating that other factors also contribute to determining the sensitive subpopulation. Although some studies indicate that early stages of CBD can be reversed, the degree of reversibility and exposure levels that allow reversibility have not been characterized. Although animal models that mimic several aspects of human CBD appear to be available in the dog, monkey, mouse, and guinea pig, an animal model that mimics all aspects of CBD, in particular the progressive nature of the disease, has not been identified.

The potential of beryllium to induce developmental and/or reproductive effects has not been adequately assessed. No effect on fertility or pup survival, body weight, or skeletal formation was observed in a chronic dog feeding study. However, this study did not conduct visceral examinations of pups or monitor postnatal development. Developmental effects (increased fetal mortality, decreased fetal body weight, internal abnormalities, and delayed neurodevelopment) have been reported in the offspring of rodents following intratracheal or intraperitoneal administration of beryllium. No reproductive effects were observed in rats receiving a single intratracheal instillation of beryllium.

The areas of scientific uncertainty concerning the noncancer hazard assessment for beryllium include examination of immunologic endpoints or sensitive indicators for rickets in chronic oral studies in animals, an animal model that mimics the progressive nature of CBD in humans, and adequate oral developmental and reproductive toxicity studies.

No oral human carcinogenicity data are available. No significant increases in tumor incidence have been observed in several chronic oral carcinogenicity studies in animals (Morgareidge et al., 1975, 1977; Schroeder and Mitchener 1975a,b). However, these used beryllium doses below the MTD.

A series of follow-up epidemiological studies on beryllium processing workers (Mancuso, 1979, 1980; Wagoner, 1980; Ward et al., 1992) and on BCR registrants (Infante et al., 1980; Steenland and Ward, 1991) suggest that inhalation exposure to beryllium causes lung cancer. Scientific uncertainties in the assessment of the human carcinogenicity data include the adequacy of control for confounders such as differences in smoking habits between the exposed cohorts and comparison populations or potential occupational exposure to other lung carcinogens, the lack of personal exposure data or detailed job history data that would support quantitative exposure assessment, and the relatively small increases in lung cancer risks. Nevertheless, the increased incidence of lung cancers among workers with acute beryllium disease (presumably these workers were exposed to very high concentrations of beryllium), the higher incidence of lung cancers among workers first employed when exposure levels were very high, a consistent finding of lung cancer excesses in six of seven beryllium processing facilities, and the occurrence of the highest risks for lung cancer in plants where the risk for nonmalignant respiratory disease is the highest are indicative of a causal relationship between beryllium exposure and an increased risk of lung cancer. The data are considered limited evidence of carcinogenicity to humans.

Inhalation exposure or intratracheal administration of beryllium has resulted in lung cancer in rats and monkeys (Nickell-Brady et al., 1994; Reeves et al., 1967; Reeves and Deitch, 1969; Vorwald, 1968; U.S. EPA, 1987b, 1991b; Wagner et al., 1969). These observations support a possible causal association noted in the occupational studies. In addition, intravenous and intramedullary injection induced osteosarcomas in rabbits and possibly in mice (U.S. EPA, 1987b, 1991b). These data are considered sufficient evidence of carcinogenicity to animals.

Based on the weight of evidence (limited human and sufficient animal), beryllium can be classified as a probable human carcinogen (B1) according to the 1986 guidelines. According to the 1996 proposed guidelines, inhaled beryllium would be characterized as a "likely" carcinogen; the human carcinogenic potential of ingested beryllium cannot be determined because of inadequate data.

The lack of adequate oral carcinogenicity data is an area of scientific uncertainty for this assessment.

6.2. DOSE RESPONSE

A quantitative estimate of human risk as a result of low-level chronic beryllium oral exposure is based on animal experiments, since no adequate human oral exposure data are available; the gastrointestinal system appears to be the primary target of toxicity in dogs. Quantitative estimates of human risk as a result of low-level chronic beryllium inhalation exposure are based on human data. The lung appears to be the primary target of toxicity and carcinogenicity in human and animal inhalation studies.

The human chronic dose of ingested beryllium considered to be safe (RfD) is $2\text{E-}3$ mg/kg-day. This is 1/300 of the BMD10, using small intestinal lesions in a long-term dog study as the indicator of adverse effects. The BMD10 dose is the 95% lower confidence limit of the dose that produces a 10% incidence of small intestinal lesions. It was calculated using data from the four beryllium dose groups and the control group.

The overall confidence in the RfD assessment is low to medium, derived from medium confidence in the principal study and low to medium confidence in the database. Beryllium was administered by a relevant route (oral) at multiple dose levels for a chronic duration and demonstrated effects at two dose levels. Relatively comprehensive histopathologic evaluations were conducted. However, there were small groups of animals (5/sex/dose), early mortality at the high dose level, no evidence of randomization or control for potential litter effects, and no measure of immune response or function, the critical endpoint by the inhalation route. Confidence in the database is low to medium because there is only one chronic dog study showing adverse effect levels; other chronic studies in rodents demonstrated NOAELs at the highest doses tested. Confidence in this assessment is improved over the earlier version on IRIS because of the inclusion of additional chronic studies in rats and dogs.

The human chronic air concentration (RfC) considered to be safe is $2\text{E-}2$ $\mu\text{g}/\text{m}^3$. This concentration is 1/10 of the adjusted adverse effect level for beryllium sensitization and CBD in workers (Kreiss et al., 1996).

The overall confidence in the RfC assessment is medium. The RfC is based on an occupational inhalation study performed with a moderate to large group size (136 subjects screened) in which sensitive measures were used to identify the affected population (Kreiss et al., 1996). No NOAEL was identified in this study, but a NOAEL slightly below the LOAEL(HEC) was suggested in a study using less sensitive methods of diagnosing CBD in a population exposed to high levels of beryllium in ambient air (Eisenbud et al., 1949). The poor quality of the exposure monitoring in the co-principal studies decreases the confidence in the principal studies to medium. The confidence in the database is also medium. A common limitation in the database is the lack of adequate exposure monitoring in the epidemiology studies and some uncertainty regarding the mechanism (and beryllium exposure levels) associated with the progression to CBD in beryllium-sensitized individuals. Several human and animal studies are currently being conducted that may provide additional information on the mechanisms of action and data that would be useful for dose-response assessment. Although no inhalation developmental or multigenerational reproductive studies were available for beryllium, no reproductive effects were observed in an intratracheal reproduction study in animals at exposure levels above those causing CBD (Clary et al., 1975). In addition, the unusually low level at which CBD occurs, together with the low systemic distribution of inhaled beryllium, mean that any developmental effects would occur at levels much higher than those causing CBD. Reflecting the medium confidence in the principal studies and database, confidence in the RfC is medium.

The Agency based the estimate of human cancer risk from inhalation exposure on the epidemiological study of beryllium processing workers by Wagoner et al. (1980). The estimated lung cancer risk is $2.4\text{E-}3$ for exposure to 1 $\mu\text{g}/\text{m}^3$. Although newer studies are available, they share a major scientific uncertainty with the Wagoner et al. (1980) study—the lack of personal

monitoring data or detailed job history data from which exposure could be fully assessed. NIOSH, however, has recently completed a lung cancer study in a large cohort of beryllium processing workers. This study developed an exposure matrix and calculated airborne beryllium exposure concentrations, and may therefore provide the best basis for a quantitative cancer estimate. The study is currently in peer review, and will be evaluated as the basis for a new quantitative estimate when available.

The relation between the quantitative cancer and noncancer risk estimates given above can be determined by calculating the cancer risk to people hypothetically exposed continuously via inhalation to the RfC. The lifetime cancer risk would be $5E-6$ for inhalation, which is normally considered to be negligible.

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8. APPENDICES

APPENDIX A. BENCHMARK DOSE FOR RfD

(1) *Computational Models-Quantal Data for Small Intestine Lesions in Male and Female Dogs (Morgareidge et al., 1976)*

The polynomial mean response regression model (THRESH, I.C.F. Kaiser, 1990), the exponential polynomial model, and the Weibull model were used to fit data by the maximum likelihood method. The following are the forms of the three equations used.

$$\text{THRESH} \quad P(d) = 1 - \exp[-q_1(d-d_0)^1 - \dots - q_k(d-d_0)^k]$$

Exponential

$$\text{Polynomial} \quad P(d) = 1 - \exp[-q_1(d)^1 - \dots - q_k(d)^k]$$

$$\text{Weibull} \quad P(d) = 1 - \exp[-\beta (d)^j]$$

where:

d = dose

d_0 = threshold

$P(d)$ = probability of a response (health effect) at dose d

$q_1 \dots q_k, d_0, \alpha, \beta, k$ = estimated parameters

For data input to THRESH and polynomial exponential models, the degree of the polynomial $k = 2$ gave the best representation of the data, and the response type was extra $[P(d) - P(0)]/1 - P(0)$. For the THRESH model, a threshold was estimated.

(2) *Data*

| Group | Dose (mg/kg-day) | # Response/# animals |
|-------|---------------------|----------------------|
| 1 | 0 | 0/10 |
| 2 | 0.026 | 0/10 |
| 3 | 0.135 | 0/10 |
| 4 | 1.2 | 1/10 |
| 5 | 14.8 | 9/10 |

Doses are average of male and female doses. Incidence is combined for males and females.

(3) Model Fit

Model fit was judged by the P-values associated with the χ^2 goodness-of-fit generated by the models.

(4) Results

| Model | BMD10 (mg/kg-day) | MLE (mg/kg-day) | Estimated parameters | P-value | χ^2 Goodness- of -fit | Degrees of freedom |
|---------------------------|----------------------|--------------------|---|---------|----------------------------------|-----------------------|
| Exponential polynomial | 0.46 | 1.4 | q1 = 6.9E-2 q2 = 5.9E-3 | 0.94 | 0.13 | 2 |
| THRESH | 0.47 | 1.2 | q1 = 9.4E-2 q2 = 4.3E-3 d ₀ = 1.4E-1 | 1.0 | 8.7E-18 | 1 |
| Weibull | 0.46 | 1.3 | $\alpha = 0$ $\beta = 7.3E-2$ | 0.96 | 0.08 | 2 |

(5) Discussion

There was good correlation among the three models for the BMD10. The BMD10 of 0.46 (rounded to 0.5 mg/kg-day) is used for further quantitation of the RfD.

APPENDIX B. SUMMARY OF AND RESPONSE TO EXTERNAL PEER REVIEW COMMENTS

The Toxicological Review for Beryllium and Compounds and all individual beryllium assessments have undergone both internal peer review performed by scientists within EPA or other Federal agencies and a more formal external peer review performed by scientists chosen by EPA in accordance with U.S. EPA (1994a). Comments made by the internal peer reviewers were addressed prior to submitting the documents for external peer review and are not part of this appendix. The external peer reviewers were tasked with providing written answers to general questions on the overall assessment and on chemical-specific questions in areas of scientific controversy or uncertainty. In addition, the external peer reviewers met to discuss the individual beryllium assessments; issues raised at this meeting are also discussed below. A summary of comments made by the external reviewers and EPA's response to these comments follows. The nine external peer reviewers (see Contributors and Reviewers) recommended that this document and the accompanying assessments be accepted with revisions.

The external peer reviewers offered editorial comments and many minor but valuable suggestions; these have been incorporated into the text to the extent feasible. Substantive scientific comments are addressed below. Several reviewers provided citations and/or copies of papers they would like to see added to the Toxicological Review; studies that supported the hazard identification and dose-response assessments have been incorporated into the document.

(1) Comments on General Questions

Question 1. Are there other studies that should be included as additional or supporting studies for the RfD? (This assumes the RfD is based on the Morgareidge et al. dog study [1976]).

Comments: Three reviewers thought the studies cited for the RfD and oral toxicity of beryllium were appropriate. One reviewer thought the document could also draw upon the larger metal literature for general information relating to the biokinetics/bioavailability of beryllium. No important papers were discovered in independent literature searches conducted by one reviewer.

Response to Comments: The revised Toxicological Review bases the RfD on the Morgareidge et al. (1976) chronic feeding study in dogs. Chronic studies in mice and rats serve as the supporting studies. When appropriate, reference is made to the larger body of information on metals.

Question 2. Are the uncertainty and modifying factors appropriate for the RfD? (Comments by reviewers refer to the RfD based on a benchmark dose approach for the gastrointestinal lesions in the Morgareidge et al. [1976] dog study.)

Comments: Five reviewers agreed that a range of 100 to 300 for the uncertainty factor seemed prudent or reasonable. While these reviewers agreed that 10-fold factors for

intraspecies and interspecies extrapolation were needed, there was less agreement as to whether the database uncertainty factor (UF) should be 1 or 3. The reviewers agreed that a UF for database deficiencies should be reviewed by EPA. Other reviewers felt it was outside their expertise to comment.

Response to Comments: There is a 300-fold UF applied to the benchmark dose for small intestinal lesions in male and female dogs. This UF is composed of 10-fold each for intra- and interspecies extrapolation and a threefold factor for database deficiencies. Database gaps include lack of adequate studies for assessment reproductive and developmental toxicity (including multigenerational studies and studies on male reproductive toxicity, teratology, and postnatal development) owing to beryllium's possible crossing of the placenta and greater absorption in young animals. In addition, oral studies examining immunologic endpoints, the most sensitive endpoint by the inhalation route, are lacking.

Question 3. Is the confidence statement appropriate for the RfD? (Comments by reviewers refer to the RfD based on a benchmark dose approach for the gastrointestinal lesions in the Morgareidge et al. [1976] dog study.)

Comments: Three reviewers agreed that confidence of low to medium for an RfD based on the Morgareidge et al. (1976) dog study seem reasonable.

Response to Comments: Confidence statements for the RfD reflect the above comments.

Question 4. Was the RfC based on the most appropriate critical effect and study (studies)?

Comments: The peer reviewers felt that beryllium sensitization and progression to CBD were the most appropriate critical effects and recommended using Kreiss et al. (1996) and Eisenbud et al. (1949) as co-principal studies. The reviewers felt that the beryllium air concentrations measured retrospectively over a 2-week period in Cullen et al. (1987) may not be representative of exposures over the previous 20 years, and suggested that this study should not be used as a principal study. One reviewer felt that the critical effect should be described as "subclinical beryllium lung disease (SBLD)" rather than CBD. In addition, the document should include a discussion of SBLD, in particular that individuals with SBLD appear to be at risk for developing symptoms of CBD, the transition from SBLD to CBD does not require additional beryllium exposure, and not all individuals with SBLD will develop CBD.

Response to Comments: The critical effect for the RfC was changed from beryllium sensitization to beryllium sensitization and progression to CBD based on the LOAEL identified in the Kreiss et al. (1996) study and the NOAEL from the Eisenbud et al. (1949) study. The Cullen et al. (1987) study was used as a supporting study rather than a principal study. A discussion of the subclinical aspects of CBD and the potential progression to overt CBD (with or without additional beryllium exposure) are discussed in the document.

Question 5. Are there other data that should be considered in developing the uncertainty factors or modifying factors for the RfC?

Comments: Three reviewers recommended adding an additional uncertainty factor to account for uncertainties in the database, in particular the poor quality of exposure monitoring data. Two reviewers recommended using a 3 uncertainty factor and one reviewer recommended a total uncertainty factor of greater than 3 but less than 10. At the peer review panel meeting, one reviewer voted to increase the uncertainty factor to 10 (although he did not discuss the uncertainty factor in his written comments). Three reviewers were comfortable with a total uncertainty factor of 3. Two reviewers did not comment on the uncertainty factor.

Response to Comments: EPA agreed with the recommendation of the majority of the peer reviewers and increased the total uncertainty factor to 10; 3 for use of a LOAEL and 3 for database limitations.

Question 6. Does the Confidence Statement for the RfC present a clear rationale and accurately reflect the utility of the studies chosen, the relevancy of the effects to humans, and the comprehensiveness of the database, and does the statement make sufficiently apparent all the underlying assumptions and limitations of the RfC assessment?

Comments: Three reviewers agreed with the confidence limits (medium for principal studies, high for database, and medium-to-high for the RfC). Three reviewers recommended changing the confidence in the database to medium and noting that there are several ongoing human and animal studies. Three reviewers did not comment on the confidence statement.

Response to Comments: In response to the peer review comments, the confidence in the database was changed to medium; the confidence in the RfC was changed to medium to reflect the medium confidence in both the principal studies and the database.

Question 7. For the cancer assessment, are the tumors biologically significant and relevant to human health?

Comments: The lung cancer SMRs in the human occupational studies and BCR entrant studies were felt to be relevant by three reviewers. One reviewer felt that the reticulum cell sarcomas seen in the rat study are of dubious significance to humans and that these tumors should be examined as a combined incidence across tissues rather than on a tissue-by-tissue basis; this point also was raised by one reviewer and in the peer review. One reviewer had reservations regarding the human studies, as expressed in comments on the specific question regarding changing the weight-of-evidence classification for carcinogenicity. The remaining reviewers did not comment.

Response to Comments: The reticulum cell sarcoma data have been further analyzed as suggested and found to be not significant statistically; this information has been added to the document. Further discussion regarding the strengths and limitations of the human data has been added to the document.

Question 8. Does the cancer weight-of-evidence statement present a clear rationale?

Comments: Two reviewers said yes. One reviewer commented that the IRIS summary of the animal data focused on the oral data, but that the inhalation animal data should also be included as they provide support for the carcinogenicity assessment. The other reviewers did not respond to this question.

Response to Comments: The inhalation carcinogenicity studies in animals have been incorporated into the IRIS summary.

(2) Comments on Chemical-Specific Questions

Question 1. Is there a minimum database for derivation of an RfD? Do you think the present IRIS RfD (Schroeder and Mitchener, 1975) meets minimum database requirements? Do you agree with the "not verifiable" status recommended in the draft document reviewed by the panel? Should the Morgareidge et al. rat (1975, 1977) or dog (1976) studies be used as the bases of the RfD? What is the most appropriate critical effect and study/studies?

Comments: The majority of the reviewers thought the database was sufficient to establish an RfD as per EPA guidelines. There are four chronic studies available in three species (dogs, rats, mice) by a relevant route of exposure. Although each study has difficulties and alone would be considered deficient by contemporary toxicology standards, collectively they establish a range of doses that is unlikely to evoke noncancer toxicity. Although the Morgareidge dog study (1976) was not published as a peer review paper and did not measure immune response or function (an endpoint important by the inhalation route), the reviewers felt it was a properly conducted, multiple-dose chronic oral study with complete histopathology that showed effect levels. The dog study is preferred over the rat studies for several reasons: the rat is typically a poorer model than the dog for the absorption kinetics of elements in humans, and the dog study used lower Be doses/kg body weight than the rat studies and showed a dose-response for an adverse effect. However, the reviewers suggested that the Agency review the Morgareidge dog study to possibly establish a BMD-based RfD based on GI tract lesions, and have a veterinary pathologist review the pathology data (specifically gastrointestinal lesions). Since there is an effect in the dog study, the issue of a free-standing NOAEL is moot. It was noted however, that in the past EPA has derived RfDs with only NOAELs from several studies (or even a series of NOAELs from just one study). The Schroeder and Mitchener studies (1975) used doses that were too low to establish an effect level. The Morgareidge rat study was considered inconclusive because not all tissues or animals were analyzed.

One reviewer further suggested that various dose-response curves (quantal linear, Weibull, gamma multi-hit, multistage) can be fitted to the gastrointestinal data and recommended EPA consider the quantal linear model for the gastrointestinal lesion data set (stomach, small GI, or large GI).

One reviewer thought the “not verifiable” status is reasonable as the cited studies are weak and of questionable use in “unequivocally establishing” a NOAEL and LOAEL. The Morgareidge et al. (1976) dog study appears useful for RfD derivation, although the death of one animal in the 50 ppm group, while the other animals appeared to be minimally affected, is of some concern.

Response to Comments: The RfD in the Toxicological Review is derived from small intestinal lesions in male and female dogs in the Morgareidge et al. (1976) chronic feeding study.

A board-certified veterinary pathologist reviewed the Morgareidge et al. (1976) study report (but not the slides, which are unavailable) and concluded, “...given that the GI tract lesions occurred in both the small and large intestines, occurred in most of the high-dose animals, both male and female, and occurred in animals without roundworms, it appears that the GI lesions are related to beryllium treatment rather than some other cause.” Further, the lesions that appeared to be related to treatment occurred predominantly in the small intestine and were erosive and inflammatory in nature. Treatment-related small intestinal lesions grouped together for determination of incidence data were: desquamation of the epithelium, edema, fibrin thrombi, acute inflammation, subacute/chronic inflammation, necrosis, thinning/atrophy of the epithelium, and ulceration. The lesions in the one female in the 50 ppm treatment group that was killed earlier in the study (week 70) appeared to be of the same types as those found in dogs in the 500 ppm group, suggesting to the pathologist that the lesions in this dog were treatment-related.

A BMD approach using the exponential polynomial model was applied to these data to derive the 95% lower confidence limit on dose producing a 10% response (extra risk), or the BMD₁₀, of 0.46 (MLE = 1.4; goodness-of-fit = 0.13) mg/kg-day using the mean doses for males and females and the combined incidence for small intestinal lesions. The BMD approach was chosen over the NOAEL/LOAEL approach because it utilizes all of the dose-response information and decreases reliance on the response of the one animal in the 50 ppm dose. The Weibull model, using the same inputs, determined a BMD₁₀ of 0.46 (MLE = 1.3; goodness-of-fit = 0.08) mg/kg-day. Other models were also run on these data with similar results (THRESH, BMD₁₀ = 0.47, MLE = 1.2, goodness-of-fit = 8.7E-18).

Question 2. Is it appropriate to base the RfD on soluble beryllium salts, even though beryllium oxide appears to be the most environmentally relevant form of beryllium? Since beryllium precipitates in the gut as the insoluble phosphate and is not well absorbed (< 1%), is it appropriate to use various parenteral routes to mimic the oral route of ingestion? If so, are the studies of sufficient quality to be used in risk assessment?

Comments: The reviewers agreed that it seemed reasonable to base the RfD on animal studies using soluble beryllium salts, particularly in the absence of compelling information otherwise. By analogy to other chemical elements, the chemical form of the inorganic salt most likely will modify the bioavailability, but the different salts are less likely to have different mechanisms of action and toxicities. Statements of beryllium solubility and that beryllium precipitates in the gut as insoluble phosphate may not be an adequate

generalization for predicting biokinetics in humans. However, whatever the chemical form it is accurate to say that beryllium is very poorly absorbed through the gastrointestinal tract. Parenteral administration can be useful in studying the disposition of beryllium in the body, but its usefulness in dose-response assessment is likely limited.

One reviewer noted that it is probably correct to say that oxidized forms of beryllium are the most environmentally relevant, but the document should present information to substantiate this. However, the reviewer was not aware of studies for beryllium in water that would indicate the most common form in water is the oxide.

Response to Comments: The statement about beryllium precipitating in the gut as the insoluble phosphate is not well documented and has been deleted as a generalization.

Chapter 3 states that beryllium from anthropogenic sources is generally emitted as the oxide and cites EPA's Health Assessment Document for Beryllium (1987). A citation for ATSDR's Toxicological Profile for Beryllium (1993) has also been added.

Question 3. Should the RfDs/RfCs be presented as a point estimate or as a range?

Comments: RfD (Comments by reviewers refer to the RfD based on a benchmark dose approach for the gastrointestinal lesions in the Morgareidge et al. [1976] dog study.): While one reviewer thought a range was appropriate, another preferred a point estimate with a statement that the RfD is imprecise to perhaps an order of magnitude (and that an RfD based on animal data is less precise than an RfD based on human data). Another reviewer did not have a strong opinion regarding a point estimate or range as being more appropriate, but thought the approach for beryllium should reflect that there is weak and/or uncertain information in the oral database because the studies all have questions and sources of uncertainty associated with them. Based on discussions at the meeting, one reviewer noted that a range for the RfD would arise from use of the range of uncertainty factors (100 to 300). (See also General Question 3).

RfC: Two reviewers preferred a point estimate and one of these reviewers preferred a statement that the RfC is imprecise to perhaps an order of magnitude. Two reviewers noted that there was some uncertainty associated with the exposure monitoring in the Kreiss et al. study (1996), and questioned whether it was appropriate to use a single exposure level; one reviewer thought it was appropriate to express the RfC as a range of the Eisenbud et al. (1949) and Kreiss et al. (1996) exposure levels.

Response to Comments: The RfD and RfC are presented as a point estimate with the statement that they are imprecise, perhaps to an order of magnitude. This approach is consistent with current EPA policy for the RfD/RfC.

Question 4. Does the following statement accurately reflect current knowledge: "Although a number of chronic studies in laboratories have been conducted with beryllium compounds, few have been done using modern toxicological methods and none of those in animals that are appropriate models for CBD"?

Comments: Five of the reviewers noted that an animal model that mimics all aspects of human CBD has not been identified. However, the reviewers noted that there are several adequate animal models that mimic certain aspects of CBD. The other three reviewers did not comment on the statement.

Response to Comments: In response to the comments made by the peer reviewers, the statement regarding animal models was modified. The revised statement notes that there are several animal models that adequately mimic certain aspects of human CBD. However, a laboratory animal model that mimics all features of human CBD, in particular the progressive nature of the disease, has not been identified.

Question 5. Based on more recent epidemiological follow-up studies of beryllium processing workers (Ward et al., 1992) and entrants on the BCR (Steenland and Ward, 1991), is there sufficient support for changing the weight-of-evidence classification for carcinogenicity from a B2 to a B1 carcinogen and maintaining the present quantitative inhalation carcinogenic assessment?

Comments: Two reviewers agreed that the data supported a change to B1 (probable human carcinogen), but one reviewer expressed a concern that this characterization differs from that of IARC (1993), which considered the human data sufficient, whereas EPA concluded it was limited. One reviewer expressed reservations about changing the characterization to B1, based on the reviewer's intensive review of the earlier Wagoner et al. (1980) study and impressions of the review panel's discussion of the Ward et al. (1992) study. One reviewer said B, but lacked experience to differentiate between B1 and B2. Reviewer #7 thought that beryllium should be classified in Group A. Three reviewers declined to comment. Reviewer #1 said the data do not clearly demonstrate carcinogenicity from inhalation exposure (hence not Group A) and that the choice of B1 rather than B2 may depend on analyses suggested during the peer review meeting (i.e., of the possible confounding by acid mists). One reviewer suggested that further analysis of the acid mist issue might bring EPA's assessment into agreement with IARC's, or could be used to explain the differences between the assessments.

In addition, one reviewer on the peer review panel commented that evidence for carcinogenicity by the oral route was inadequate. The peer review panel concluded that no oral risk estimate should be derived.

The majority of reviewers did not address the issue of whether to maintain the present quantitative inhalation carcinogenic assessment. One reviewer said that a quantitatively derived unit risk should not be calculated with the existing data because they are not sufficient. The reviewer recommended that quantitation be deferred until the NIOSH study with its better exposure estimates is available. One reviewer suggested that all the exposure information from the NIOSH criteria document be used with the Ward et al. (1992) data to calculate a unit risk. The peer review panel also suggested that the exposure range estimates by NIOSH that were used with the Wagoner et al. (1980) data for quantitative cancer assessment could be used with the Ward et al. (1992) data to estimate a unit risk. One reviewer pointed out that the dose conversion for the Wagoner et al. (1980) study incorporates some unstated assumptions concerning the appropriate dose metric with regard

to cumulative lifetime exposure that may not be appropriate, and that the rationale for the dose conversion should be added.

Response to Comments: Further analysis of the issues regarding potential confounding by exposure to acid mists did not clearly implicate acid mists, nor did it completely resolve the issue (see response to comments on the subsequent question regarding sulfuric and hydrofluoric acid mists). Reflecting this and other limitations in the human data, the Agency concludes that the appropriate classification is B1 rather than A. The change from B2 to B1 is appropriate, because the increased incidences of lung cancers among workers with acute beryllium disease (and therefore assumed to be exposed to very high concentrations of beryllium), the higher incidences of lung cancers among workers first employed when exposure levels were very high, a consistent finding of lung cancer excesses in six of seven beryllium processing facilities, and the occurrence of the highest risks for lung cancer in plants where the risk for nonmalignant respiratory disease is the highest are indicative of a causal relationship between beryllium exposure and an increased risk of lung cancer. A discussion regarding the difference between IARC's and EPA's conclusions regarding the adequacy of the human data has been added.

The Agency agrees that the data are inadequate for the assessment of carcinogenicity by the oral route and that no oral risk estimate should be derived. The oral toxicological review document and IRIS summary have been revised slightly to clarify this conclusion.

Use of additional exposure information from the NIOSH criteria document with the data of Ward et al. (1992) is problematic because of the lack of specific job history data in the study that would link workers with the job- and work-area specific exposure data in the NIOSH document. Similarly, use of the NIOSH exposure range estimates with the Ward et al. (1992) data to estimate a new unit risk study does not overcome a major limitation common to both the Wagoner et al. (1980) and Ward et al. (1992) studies—the lack of personal monitoring data or detailed job history data from which exposure could be fully assessed. NIOSH, however, has recently completed a lung cancer study in a large cohort of beryllium processing workers. This study developed an exposure matrix and calculated airborne beryllium exposure concentrations, and may therefore provide the best basis for a quantitative cancer estimate. The study is currently in peer review, and will be evaluated as the basis for a new quantitative estimate when available. Until that time, the current inhalation estimate will be retained. The explanation of the dose conversion for the unit risk has been revised so that it is consistent with the original explanation (U.S. EPA, 1987).

Question 6. Given that IARC (1992) has designated sulfuric acid mist a human carcinogen, is there reason to think that the elevated SMRs for lung cancer at the Lorain and Reading beryllium processing facilities were due to sulfuric and hydrofluoric acid mist, respectively, rather than to beryllium?

Comments: Three reviewers agreed that there is reason to suspect exposure to these acid mists as a potential confounder. Two reviewers said that these mists were not the principal culprits. One reviewer did not answer the question because of lack of information. Three reviewers did not address the question. The majority of reviewers, and the peer review

panel as a whole, suggested that additional analysis of this issue be undertaken, including an investigation of what levels of sulfuric acid mist are associated with increased cancer risk, the SMRs, and the tumor types as compared with the beryllium data.

Response to Comments: Investigation of this issue revealed that exposure to sulfuric acid mists has not been strongly associated with lung cancer, but rather with laryngeal cancer (IARC, 1992; Sathiakumar et al., 1997). Limitations in the evidence for an association between exposure to sulfuric acid mist and lung cancer include poor or no quantitation of exposure, possible confounding by other occupational exposures and smoking, and low SMRs. The majority of lung cancer SMRs in the studies that reported a positive association between exposure to sulfuric acid mists and lung cancer were in the range of 1.18 to 1.39. The studies of lung cancer in workers exposed occupationally to beryllium and/or sulfuric acid or other acid mists do not, for the most part, categorize the type of cancer. Thus, the data are insufficient to determine whether different types of lung cancer may be associated with beryllium exposure versus sulfuric acid exposure. There are no carcinogenicity studies of sulfuric acid in animals. Information regarding the potential carcinogenicity of hydrofluoric acid was not available. IARC (1992) considered hydrofluoric acid to be a weak inorganic acid and did not assess it in the monograph on strong inorganic acids. A more detailed discussion of these findings has been added to the toxicological review document, and a brief discussion has been added to the IRIS summary. The results of this investigation do not change the Agency's conclusions regarding the cancer weight-of-evidence classification for beryllium.

Question 7. Based on the overall evidence from in vivo and in vitro studies, can one say unequivocally that beryllium is not a genotoxic carcinogen?

Comments: One reviewer said yes, while four other reviewers said no but indicated that beryllium is probably acting by a nongenotoxic mechanism, and four reviewers felt this question was outside their area of expertise.

Response to Comments: The document is consistent with the reviewers' conclusions.

Question 8. Is it appropriate to base the cancer assessment on soluble beryllium salts, even though beryllium oxide appears to be the most environmentally relevant form of beryllium?

Comments: One reviewer noted that the qualitative and quantitative cancer assessments were based on human occupational studies and animal studies involving exposure to a variety of beryllium compounds and the metal, and that the evidence suggests that the various forms appear to be carcinogenic. One reviewer stated that lung cancer has been observed in animals dosed with soluble salts by the respiratory route. The other reviews did not specifically address this issue with regard to cancer assessment.

Response to Comments: The occupational studies involved exposure to various soluble and insoluble forms of beryllium, as did the positive animal studies (inhalation, intratracheal, intravenous, and intramedullary). Thus, carcinogenicity does not appear to be a property exclusive to the soluble salts.